National Institute for Health and Care Excellence

Final

Ovarian cancer: identifying and managing familial and genetic risk

[K] Benefits and risks of surveillance

NICE guideline NG241

Evidence reviews underpinning recommendations 1.8.18 to 1.8.20 (including information on surveillance in table 3) and research recommendation 4 in the NICE guideline

March 2024

Final

This evidence review was developed by NICE

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Benefits and risks of surveillance

Review question

What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

Introduction

Not all women can undergo risk reducing surgery as they may wish to preserve their fertility, choose to avoid surgery or are not well enough to undergo surgery. The use of surveillance in this high-risk group is different to its application in the general population as the burden of disease and the biology of ovarian cancer is different. The proposed benefit of surveillance for ovarian cancer in those with a familial cancer risk is to improve survival by detecting disease earlier. Surveillance however is not without risks as it can give false positive results leading to unnecessary surgery and false negative results in which a cancer is missed. This review investigates the current evidence base as to the risks and benefits of ovarian cancer surveillance in those with a familial cancer risk.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women at increased risk of familial ovarian cancer

Intervention	Regular (for example annual) screening for ovarian cancer using a combination of:
	• CA125 test
	• Imaging:
	  ○ transvaginal ultrasound (TVUS)
	  ○ MRI
	  ○ CT
	• Prediction rules:
	  ○ Risk of Ovarian Cancer Algorithm test (the ROCA Test)
	  ○ multi-maker algorithms
	  ○ mathematical evaluation (other algorithms or techniques)

Comparison	• No surveillance
	• Risk reducing treatments:
	  ○ surgery
	  ○ chemoprevention

Outcomes	**Critical**
	• Quality of life
	• Survival:
	  ○ cancer specific survival
	  ○ overall survival
	  ○ recurrence free survival (surrogates: zero residual after definitive ovarian cancer treatment)

	• Ovarian cancer:
	  ○ incidence
	  ○ stage at diagnosis
	  ○ screen detected and interval related cancers
	  ○ histological type
	Important
	• Treatment related adverse effects and test related morbidity such as:
	  ○ anxiety
	  ○ investigation of false positive results
	• Psychological outcomes and wellbeing including:
	  ○ patient satisfaction
	  ○ acceptability and attitudes
	• Healthcare use

CA125: cancer antigen 125; CT: computer tomography; MRI: magnetic resonance imaging; ROCA: risk of ovarian cancer algorithm; TVUS: transvaginal ultrasound

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

Two studies were included for this review: 1 randomised controlled trial (RCT; Lai 2016) and 1 prospective cohort study (Mai 2020).

The studies compared ovarian cancer screening with usual medical care (Lai 2016) and with risk reducing salpingo-oophorectomy (RRSO; Mai 2020), respectively.

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix K.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Lai 2016 (PLCO trial)	N=22355 with family history of breast	OCS Baseline pelvic	Usual medical care	• Survival ○ overall survival	Most patients did not have genetic tests,

Study	Population	Intervention	Comparison	Outcomes	Comments
RCT USA	or ovarian cancer Age, mean (SD), years: OCS 62.8 (5.4); usual medical care 62.9 (5.5)	ultrasound and serum CA125, with subsequent annual pelvic ultrasound for an additional 3 years, and annual CA-125 for 5 years	No details reported other than that the women did not undergo cancer specific screening	○ overall mortality ○ ovarian cancer specific mortality • Ovarian cancer ○ stage at diagnosis	so their level of cancer risk is uncertain. It is likely that they are a heterogeneous group with an intermediate to moderate cancer risk
Mai 2020 (GOG-0199 study) USA Prospective cohort	N=1780 with family history of ovarian cancer or ≥ 20% probability of pathogenic *BRCA1/2* variant Age, mean (SD), years: not reported Age-groups (years, %): RRSO 30-39 = 17.08%, 40-49 = 42.53%, 50-59 = 30.25%, 60-69 = 8.36%, >=70 = 1.78%; OCS 30-39 = 27.13%, 40-49 = 31.78%, 50-59 = 29.8%, 60-69 = 9.9%, >=70 = 1.39%	<u>OCS</u> Participants were screened according to the ROCA Test, with CA125 measurements and the ROCA Test score calculations every 3 months and annual transvaginal ultrasound	<u>RRSO</u> Participants underwent the protocol-defined procedure within 90 days of enrolment. Hysterectomy was performed electively per patient and physician discretion	• Quality of life ○ MOS SF-36 ○ IES overall • Anxiety ○ STAI • Psychological outcomes and wellbeing ○ CES-D	

CES-D: The Center for Epidemiology Studies Depression Scale; GOG: The Gynecologic Oncology Group trial; IES: The Impact of Events Scale (IES); MOS SF-36: The Medical Outcome Study Short Form-36; OCS: ovarian cancer screening; PLCO: The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; ROCA: Risk of Ovarian Cancer Algorithm; RRSO: risk reducing salpingo-oophorectomy; SD: standard deviation; STAI: Spielberger State-Trait Anxiety Inventory

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Summary of the evidence

There was a lack of randomised trials or observational studies comparing different surveillance protocols in women at increased risk of familial ovarian cancer. The evidence consisted of 1 randomised and 1 observational study comparing surveillance with usual medical care or risk-reducing surgery. No evidence was identified for recurrence free survival, ovarian cancer incidence, screen detected and interval related cancers, histological types, investigation of false positive results, patient acceptability and satisfaction and healthcare use outcomes.

Ovarian cancer screening versus usual medical care

Very low quality evidence showed no important difference between the screening and usual medical care groups in terms of overall mortality, ovarian cancer specific mortality and proportion of ovarian cancers that were stage I or II. However, very low quality evidence showed that overall survival was improved in the screening group compared to the usual medical care group.

RRSO versus ovarian cancer screening

Moderate quality evidence showed no important differences in terms of different quality of life, anxiety or depression measures between women who received risk-reducing salpingo-oophorectomy and cancer screening.

See appendix F for full GRADE tables.

Economic evidence

Included studies

Four economic studies were identified which were relevant to this review (Bommer 2022, Muller 2018, Philpott 2023, Yamauchi 2018).

A single economic search was undertaken for all topics included in the scope of this guideline. See supplementary material 2 for details.

Excluded studies

Economic studies not included in this review are listed, and reasons for their exclusion are provided in Supplement 2.

Summary of included economic evidence

The systematic search of the economic literature undertaken for the guideline identified the following studies:

- One Swiss study on the cost-utility of intensified surveillance (age-related imaging procedures and gynaecological consultations) for a cohort of female *BRCA* genetic mutation carriers aged 40 years (Bommer 2022);
- One German study on the cost-utility of intensified surveillance (half-yearly palpation and ultrasound, yearly mammography, and breast magnetic resonance imaging) for a cohort of female *BRCA* mutation carriers aged 30 years (Muller 2018);
- One UK study on the cost-utility of surveillance (the ROCA Test for a cohort of *BRCA* genetic mutation carriers aged 35 years (Philpott 2023);
- One Japanese study on the cost-utility of surveillance (once a year mammogram, magnetic resonance imaging, and examination) for a cohort of female *BRCA* genetic mutation carriers aged 35 years (Yamauchi 2018).

See the economic evidence tables in appendix H. See Table 3 for the economic evidence profile of the included studies.

Table 3: Economic evidence profile of a systematic review of economic evaluations of intensified surveillance (IS) for women *BRCA* mutation carriers

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	Effect (QALYs)	Cost effectiveness	
Bommer 2022 Switzerland	Minor [2]	Partially [3]	Modelling study (Markov) Female *BRCA* mutation carriers aged 40 years Time horizon: 60 years (lifetime) IS: Age-related imaging procedures and gynaecological consultations Comparators: Preventative bilateral mastectomy (PBM); preventative bilateral salpingo-oophorectomy (PBSO); PBM plus PBSO; chemoprevention with Tamoxifen (CP) Results presented for *BRCA1* and *BRCA2* carriers, separately	*BRCA1* IS vs CP: £2,534 PBM: £14,898 PBSO: £16,645 PBM & PBSO: £37,787 *BRCA2* IS vs CP: £3,012 PBM: £13,891 PBSO: £18,517 PBM & PBSO: £24,240	*BRCA1* IS vs CP: - 0.76 PBM: - 2.8 PBSO: - 2.31 PBM & PBSO: - 4.76 *BRCA2* IS vs CP: - 1.33 PBM: - 2.06 PBSO: - 2.06 PBM & PBSO: - 2.06	IS dominated by all other options	-The probability of IS being cost-effective at a willingness-to-pay (WTP) from £0 to £58,445/QALY gained: 0.00 -Changes in ovarian cancer (OC) incidence after primary breast cancer (BC), PBSO costs, hazard ratio of PBSO, PBM costs with implant reconstruction, costs of implant replacement, utility values of IS and CP have the most effects on the incremental cost-effectiveness ratios (ICERs). However, the conclusions were unchanged.
Muller 2018 Germany	Minor [4]	Partially [5]	Modelling study (Markov) Female *BRCA* mutation carriers aged 30 years Time horizon: 75 years (lifetime) IS: Half-yearly palpation and ultrasound, yearly mammography, and breast magnetic	IS vs PBM + PBSO at age 30: £14,585 PBM + PBSO at age 40: £13,334 PBSO: £9,706 PBM: £7,429	IS vs PBM + PBSO at age 30: - 2.7 PBM + PBSO at age 40: - 2.32 PBSO: - 1.75 PBM: - 1.31	IS dominated by all other options	-The probability of IS being cost-effective at WTP of £45,447/QALY gained: 0.00 -The results were robust, including changes in cancer incidence, mortality, utility assumptions, the efficacy of surgical options, the discount rate, differentiating between 'ovarian cancer' (<stage 4)

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	Effect (QALYs)	Cost effectiveness	
			resonance imaging Comparators: PBM; PBSO; PBM+PBSO at age 40; PBM+PBSO at age 30				and 'recurrent ovarian cancer' (stage 4) states - Only in case of a lower OC incidence or both OC and BC incidence, does PBM + PBSO at age 40 result in lower costs, but PBS + PBSO at age 30 remains the cost-effective option -Assuming that the utility after prophylactic surgery increased to that of a healthy woman within a period of 25 years (base-case: 5 years), the ICER of PBM + PBSO at age 40 (vs PBM + PBSO at age 30): £6,272/QALY
Philpott (2023) UK	Potentially serious [6]	Directly applicable [7]	Modelling study (Markov) Female *BRCA* mutation carriers aged 35 years Time horizon: Lifetime IS: The ROCA Test Comparator: No surveillance (control women were assumed to have the option of undergoing risk-reducing salpingo-oophorectomy, remaining disease-free or developing ovarian cancer and entering the associated therapy)	-£18,340	0.179	IS dominant	-No PSA or statistical analysis for costs or QALYs, only deterministic sensitivity analyses - At the ROCA Test unit cost of £585 (base case £150), the ICER of surveillance was £987/QALY gained - Surveillance remained dominant when varying surveillance duration from 50-80 years - Only at the early-stage (stages 1/2) cancer detection rate set at 11.5% (base case: 33.3%) the ICER of

Study	Limitations	Applicability	Other comments	Incremental			Uncertainty
				Costs [1]	Effect (QALYs)	Cost effectiveness	
							surveillance increased to £971/QALY gained
Yamauchi 2018 Japan	Potentially serious [8]	Partially [9]	Modelling study (Markov) Female *BRCA* mutation carriers aged 35 years Time horizon: 35 years IS: Undefined Comparators: PBM at age 35 + PBSO at age 45; IS from age 35, PBSO at age 45; PBM at age 35 Results presented for *BRCA1* and *BRCA2* carriers, separately	*BRCA1* IS at 35 years vs PBM at age 35, PBSO at age 45: £5,345 IS from age 35, PBSO at age 45: £2,148 PBM at age 35: -£449 *BRCA2* IS at 35 years vs PBM at age 35: £6,637 PBM at age 35, PBSO at age 45: £3,226 IS from age 35, PBSO at age 45: -£4,155	*BRCA1* IS at 35 years vs PBM at age 35, PBSO at age 45: - 1.49 IS from age 35, PBSO at age 45: - 1.43 PBM at age 35: - 1.04 *BRCA2* IS at 35 years vs PBM at age 35: - 1.82 PBM at age 35, PBSO at age 45: - 0.91 IS from age 35, PBSO at age 45: - 0.65	IS not cost-effective, that is for *BRCA1* PBM at age 35 plus PBSO at age 45 was dominant, and for *BRCA2* PBM at age 35 was dominant	Findings robust to model inputs, including probabilities and costs. However, using lower values for some utilities for preventative surgical procedures resulted in changes in results that favoured IS, but results were not reported.

Abbreviations: BC: Breast cancer; CP: Chemoprevention; ICER: Incremental cost-effectiveness ratio; IS: Intensified surveillance; OC: Ovarian cancer; PBM: Preventative bilateral mastectomy; PBSO: Preventative bilateral salpingo-oophorectomy; QALY: Quality-adjusted life-year; WTP: Willingness-to-pay

[1] Costs were converted to UK pounds using OECD purchasing power parities (PPPs)
[2] Effectiveness for preventative options from single cohort studies, some resource use data/cost data supplemented by authors' assumptions
[3] Swiss healthcare setting, QALYs estimated
[4] Effectiveness for preventative options from single cohort studies, some local unit cost data
[5] German healthcare setting, QALYs estimated

[6] The effectiveness of ROCA, based on a single-arm trial with only a one-year follow-up, assumes that cancer downstaging results in a survival advantage. However, the evidence supporting this is limited. Additionally, some model inputs are derived from the general ovarian cancer population and these may not be generalisable to individuals with pathogenic variants. There is also limited reporting on the health economic analysis and a PSA was not performed.
[7] UK study, QALYs estimated
[8] Effectiveness for preventative options from single case-control and cohort studies; unclear reporting with some results not fully reported (for example the direction of deterministic sensitivity analysis results described in the text, but detailed results are not reported making it difficult to understand whether conclusions have changed); no probabilistic sensitivity analysis; unclear why the analysis did not consider lifetime horizon
[9] Japanese healthcare setting, QALYs estimated

Expert witness

During the development of this guidance the committee identified an ongoing economic analysis that examined the cost-effectiveness of ovarian cancer surveillance in women with pathogenic germline *BRCA1* and *BRCA2* variants. In this study the surveillance included the ROCA Test and was compared with no-surveillance (where women were assumed to have the self-determined choice of undertaking risk-reducing surgery). The analysis focussed on reporting the clinical results from the surveillance trial (ALDO) but also included the cost-effectiveness as a secondary outcome.

At the time of the evidence consideration by the committee the analysis was still unpublished. Since this was an area where the committee was considering making a recommendation, they agreed that it was essential to understand the analysis. As a result, the committee invited an expert witness from London School of Economics to present the analysis. The testimony covered the cost-effectiveness of surveillance for a population at high risk of ovarian cancer in the ALDO trial. A copy of the completed expert testimony form is provided in appendix L.

Since the presentation to the committee the analysis was published and is included in the existing economic evidence review. For details see the economic evidence table in appendix H and Table 3 for the economic evidence profile for this study.

Economic model

No economic modelling was undertaken for this review because a recent economic study already explored the cost-effectiveness of a surveillance strategy that the committee recommended. Moreover, the identified effectiveness evidence was insufficient to develop a more informative economic model.

Evidence statements

Economic

- Evidence from one UK cost-utility analysis based on modelling suggests that surveillance using the ROCA Test for female *BRCA* mutation carriers was dominant, resulting in lower costs and higher QALYs, compared to no surveillance. This study was directly applicable to the NICE decision-making context and was characterised by potentially serious limitations (Philpott 2023).
- Evidence from three non-UK cost-utility analyses based on modelling suggests that surveillance for female *BRCA* mutation carriers is not cost-effective compared to preventative surgical management. All studies were non-UK and are partially applicable to the NICE decision-making context. Two studies had minor limitations (Bommer 2022, Muller 2018), and one study had potentially serious limitations (Yamauchi 2018).

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Quality of life and overall survival were prioritised as critical outcomes by the committee because deferring risk reducing treatments in favour of surveillance may have a negative impact on overall survival – but this choice might be made for quality of life reasons, for example preservation of fertility. Similarly, surveillance compared to no surveillance or treatment could have a positive impact on overall survival. Cancer specific and recurrence

free survival were also identified as critical outcomes because the aim of surveillance is to identify ovarian cancer at a pre-symptomatic stage when it is more treatable.

Incidence of ovarian cancer, screen detected and interval related cancers were chosen as critical outcomes because they indicate whether surveillance picks up pre-symptomatic ovarian cancers (screen detected) or whether they present as symptomatic between surveillance visits (interval cancers). Stage at diagnosis and histological type were also critical outcomes because they indicate the likely prognosis and response to treatment of any cancers detected.

The committee agreed that treatment related adverse effects and test related morbidity should be important outcomes. This is due to the potential anxiety associated with waiting for surveillance test results and the possible harms associated with investigation of false positive results.

Psychological outcomes and wellbeing such as patient satisfaction, acceptability and attitudes were also chosen as important outcomes because the choice of surveillance or risk reducing treatment is a trade off between harms of risk reducing treatment such as infertility and early menopause and the risk of ovarian cancer. This trade-off will likely depend on the individual's attitudes and other factors such as age.

The committee agreed that healthcare use should be an important outcome as surveillance typically requires repeated tests and healthcare appointments.

The quality of the evidence

The quality of the evidence from the included studies was assessed with GRADE and was rated as very low to moderate mainly due to serious risk of bias of individual studies and imprecision. One of the studies also had very serious indirectness because its participants did not have assessment of carrier probability or genetic testing and likely represented an intermediate to moderate risk group.

The committee discussed that there were not many studies that were identified as evidence and that there were limitations in the applicability of the populations used in the studies and in the comparisons that they were investigating. Due to the uncertainty in evidence the committee drew on their experience when making recommendations as well as expert testimony on the cost-effectiveness of surveillance and evidence from evidence review L on the diagnostic performance of difference surveillance protocols.

Benefits and harms

Information about surveillance for people who choose to delay or not have risk-reducing surgery (ovarian cancer surveillance)

The committee discussed the evidence that compared surveillance to usual care which showed a difference in overall survival favouring the surveillance group but that this did not translate into reduced ovarian cancer mortality. The committee noted that, by definition, surveillance is a health strategy that aims to detect a condition earlier rather than preventing a condition to develop. This makes it essentially inferior to risk reducing surgery which removes the organs in which ovarian cancer can develop and therefore minimises the risk of this happening (see evidence report N). This is particularly relevant to ovarian cancer which is an aggressive form of cancer which once detected is associated with serious risks. The evidence comparing surveillance to risk-reducing surgery did not show a difference in quality of life, anxiety or depression. The committee noted that this lack of difference does not mean that the two strategies are equally effective but reflected that it was reassuring to see that these outcomes were not showing an increase associated with risk-reducing surgery even though it is more invasive and induces the menopause. An advantage in undergoing

surveillance is a potential shift in ovarian cancer stage (downstaging) with cancer being detected at an earlier stage, which some of the evidence in the related evidence report on methods of surveillance (evidence report L) indicated. This is assumed to be beneficial in terms of cancer related survival because of earlier treatment. However, the committee noted that the evidence has not proven this to be the case and noted that there are no studies for people at increased risk of familial ovarian cancer designed to measure cancer related survival related to this. The committee therefore made a research recommendation to establish this (see appendix K). Given that surveillance cannot prevent cancer developing and that the only established finding is that it leads to earlier detection of cancer (without a known survival benefit) the committee decided that this strategy is clearly inferior and not an alternative to having risk-reducing surgery. They also discussed that a potential earlier detection has the disadvantage that it would not make people eligible for PARP inhibitors which is a class of drugs used in cancer therapy for people at late stage cancer, specifically targeting tumours with certain DNA repair deficiencies, such as those caused by mutations in the BRCA genes. PARP stands for Poly (ADP-ribose) polymerase, which is an enzyme involved in DNA repair. This could save lives but is not prescribed for low stage cancers. The committee concluded that surveillance should only be considered for people who delay surgery and the committee agreed that this should be made clear to the person before a decision on surveillance is made.

Given that the committee decided that surveillance should be an option for those delaying risk-reducing surgery they wanted to ensure that people were given the information that they need to make an informed choice. The committee therefore made recommendations to inform the person that their risk of developing cancer can only be reduced by risk-reducing surgery and that delaying it should therefore only be short-term. Healthcare professionals should also advise that surveillance does not decrease the risk of developing cancer. That it is therefore not an alternative to risk-reducing surgery (which the committee discussed is a common misconception) because there is little evidence on whether this leads to improved outcomes and saves lives. They also agreed to explain to the person what surveillance would involve and that there is the possibility that they may receive a false positive result (which will lead to anxiety and possibly unnecessary surgery) or false negative result (which could lead to reassurance and a potential cancer not being managed). Given the discussion above it should be emphasised to the women that surveillance is not an alternative to risk reducing surgery and that there are uncertainties about whether or not earlier detection of ovarian cancer leads to improved outcomes. The committee noted that the need of information provision in this topic, was also consistent with the qualitative evidence in evidence review A which also highlighted that people particularly valued information related to surveillance (see the relevant themes and subthemes in evidence review A – information and support).

Surveillance by the familial cancer multidisciplinary team for people who choose to delay or not have risk-reducing surgery

Whilst there were uncertainties about mortality, the majority of the committee was convinced by the evidence of downstaging as the deciding factor for their recommendation. They agreed that surveillance should be recommended as an option (i.e. a weaker recommendation) for women delaying surgery, for example those planning pregnancy. There was a discussion about responsibilities for any type of surveillance and whether there would be primary care involvement in this. Based on experience of the time constraints in primary care, the committee decided that all activities related to this would take place in secondary or tertiary care under the responsibility of the familial ovarian multidisciplinary team.

The committee outlined that risk-reducing surgery (the preferred risk management strategy) becomes relevant at difference ages (this is related to risk-reducing surgery as discussed in evidence report N) due to the different ovarian cancer risks according to age and pathogenic variant. This means therefore that surveillance should only be considered if risk-reducing surgery has been delayed beyond the time when it becomes relevant for the individual. The

committee noted the ages associated with risk-reducing surgery in accordance with the related pathogenic variant (for related evidence see evidence review N) which depend on the difference of risk of the general population at a given age and risk of people with a particular pathogenic variant. In evidence N the optimal age for this was established in an economic model and it was shown that for *BRCA1* this would be no earlier than 35, for *BRCA2* no earlier than 40, for *RAD51C, RAD51D, BRIP1* or PALB2 no earlier than 45 and for *MLH1*, *MSH2* or *MSH6* no earlier than 35 years. They decided that these would also be relevant for ovarian cancer surveillance for people with all pathogenic variants apart from *MLH1*, *MSH2* or *MSH6* which is associated with Lynch syndrome and based on knowledge the committee were aware that people with Lynch syndrome would already be regularly surveyed.

How to survey and once yearly review

They noted that a published economic model on surveillance using serial 4-monthly CA125 longitudinal testing using an algorithm (the ROCA Test) testing showed it to be a cost-effective strategy (see below and expert witness testimony in Appendix L). Based on this evidence, if a person is at risk of developing ovarian cancer and chooses to delay or not have risk-reducing surgery and if surveillance is being carried out, the committee recommended that the familial ovarian cancer multidisciplinary team should carry out serial 4-monthly CA125 longitudinal testing using an algorithm. They gave the ROCA Test as an example because they were aware that other such algorithms are in use or in development and did not want to be prescriptive about any other particular algorithm that may be developed as long as it has demonstrated accuracy. They noted the organisation of this would require the familial ovarian cancer MDT to coordinate, audit and interpret CA125 testing and review with a call and recall mechanism.

To ensure that it remains clear to the person that surveillance would not prevent them developing cancer and is not an alternative to risk-reducing surgery, the committee decided that there should be a review to discuss the recommendation of having risk-reducing surgery (see evidence review N) at least once a year.

Research recommendation

Due to the lack of evidence on long-term outcomes in people at risk of ovarian cancer the committee prioritised this topic for a research recommendation (see appendix K).

Cost effectiveness and resource use

There were four existing economic studies on the cost-effectiveness of surveillance in female *BRCA* genetic mutation carriers.

Only one study was conducted in the UK and it assessed the cost-utility of 4-monthly surveillance using the ROCA Test. This study was directly applicable to the NICE decision-making context but was characterised by potentially serious methodological limitations. The committee received expert testimony on this health economic model but questioned the conclusion that cancer stage shift leads to lives saved. In the model, the effectiveness of the ROCA Test was from a single arm trial with a one-year follow-up (ALDO) which showed downstaging in ovarian cancer.

Control arm cancer stage distribution was from the published literature. The model applied the same stage specific survival for the ROCA Test arm and the control arm. The committee discussed the credibility of this assumption. For example, it was noted that the evidence from the UKCTOCS trial suggested that ovarian cancer stage shift does not translate into survival gains. However, it was acknowledged that the ALDO study which informed the economic analysis included a high-risk population and that there may be a potential for stage shift to lead to a survival benefit.

The committee explained that due to biological differences, the proportion of high-grade ovarian cancer is greater in people with pathogenic variants such as *BRCA*, when compared with the general ovarian cancer population. There may also be differences in how responsive people with high grade serous pathogenic variants are to chemotherapy when compared with people with high grade serous cancers but who are not pathogenic variant carriers. Such differences between ovarian cancers in the general population and in people who are pathogenic variant carriers make it difficult to extrapolate from data on stage shift and survival benefit in the general ovarian cancer population.

The committee also discussed current PARP inhibitor funding arrangements and that ovarian cancer downstaging observed in the ALDO study may mean that some people may not be eligible for treatment with PARP inhibitors. This is because only advanced stage ovarian cancers are eligible for treatment with PARP inhibitors. The committee also noted that in the base-case analysis the model included PARP inhibitor costs but not outcomes which may potentially overestimate the cost-effectiveness of the surveillance arm.

It was also highlighted that there is evidence that adjuvant treatment with PARP inhibitors is associated with survival benefit in advanced stage cancers and in patients who get PARP inhibitors on relapse. In response to the above limitation, the authors have undertaken an additional sensitivity analysis which considered the potential PARP inhibitor survival benefit and the results were unchanged.

The committee also noted that the NHS reference costs do not differentiate between the extent of ovarian cancer surgery. This means that the economic analysis used the same unit cost for operating early stage versus late-stage cancer. Early-stage cancer surgery as a result of surveillance (due to downstaging) is likely to be less extensive. It may require shorter hospital stay and is less likely to need a prolonged stay on a high dependency unit or intensive care. The use of a single unit cost for ovarian cancer surgery may potentially have underestimated the cost-effectiveness of the surveillance arm.

The committee discussed the generalisability of this analysis to other genes, such as *RAD51C*, *RAD51D* and *BRIP1*. It was explained that such genes also work in the same biological pathways as *BRCA* and are more likely to have a greater proportion of high-grade serous cancers. The committee agreed that the expert testimony which presented findings from the ALDO trial on downstaging and survival benefit may potentially be generalisable to other genes too.

The remainder of the evidence was from three non-UK studies which assessed the cost-effectiveness of surveillance compared with risk-reducing surgery. None of these studies assessed the clinically effective surveillance strategy identified in the effectiveness review. As a result, these studies were of limited use to the committee decision making.

The committee explained that people who opt to delay or not to have risk-reducing surgery would be seen by clinicians once a year to revisit this option since it is the optimal choice. This annual review is current practice. It was noted that ovarian cancer surveillance's annual review would simply become part of this ongoing process, which is already in place. Consequently, implementing this recommendation is not expected to require additional resources.

The committee discussed the age cut-offs for surveillance. These age cut-offs reflect the ages at which ovarian and breast cancer risks start increasing. For example, the incidence of cancer is very low, under the age 40 in *BRCA2*. These age cut-offs also include some lead time for surveillance to pick up cancers early. It was noted that the economic evidence showed that surveillance for *BRCA* carriers was cost-effective if it was initiated at the age of 35. However, by limiting surveillance to age 40 in *BRCA2* pathogenic variants the cost effectiveness is likely to be improved further. This is because of the reduced costs in the surveillance arm due to surveillance not being initiated until age 40 in some people.

Other factors the committee took into account

The committee noted that surveillance would be a change to current practice and that therefore the infrastructure for services is not established and implementation may be a challenge and associated with a considerable resource impact. Implementation would take up clinical as well as administrative time, for example screening invites, appointments, cost of tests (the ROCA Test is currently not available in the NHS), interpretation of tests and providing the outcomes of tests.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.8.18 to 1.8.20 (including information on surveillance in Table 3) and research recommendation 4 on long-term benefits and risks of ovarian cancer surveillance in the NICE guideline.

References – included studies

Effectiveness

Lai 2016

Lai, Tiffany, Kessel, Bruce, Ahn, Hyeong Jun et al. Ovarian cancer screening in menopausal females with a family history of breast or ovarian cancer. J. Gynecol. Oncol. 27(4): e41, 2016

Mai 2020

Mai, Phuong L, Huang, Helen Q, Wenzel, Lari B et al. Prospective follow-up of quality of life for participants undergoing risk-reducing salpingo-oophorectomy or ovarian cancer screening in GOG-0199: An NRG Oncology/GOG study. Gynecol. Oncol. 156(1): 131-139, 2020

Economic

Bommer 2022

Bommer C, Lupatsch J, Bürki N, Schwenkglenks M., Cost–utility analysis of risk-reducing strategies to prevent breast and ovarian cancer in BRCA-mutation carriers in Switzerland, The European Journal of Health Economics, 23, 807–21, 2022

Muller 2018

Müller, D., Danner, M., Rhiem, K., Stollenwerk, B., Engel, C., Rasche, L., Borsi, L., Schmutzler, R., Stock, S., Cost-effectiveness of different strategies to prevent breast and ovarian cancer in German women with a BRCA 1 or 2 mutation, The European Journal of Health Economics, 19, 341-53, 2018

Phillpot 2023

Philpott, S., Raikou, M., Manchanda, R., Lockley, M., Singh, N., Scott, M., et al., The avoiding late diagnosis of ovarian cancer (ALDO) project; a pilot national surveillance programme for women with pathogenic germline variants in BRCA1 and BRCA2, Journal of medical genetics, 60, 440-49, 2023

Yamauchi 2018

Yamauchi, H., Nakagawa, C., Kobayashi, M., Kobayashi, Y., Mano, T., Nakamura, S., Arai M., Cost-effectiveness of surveillance and prevention strategies in BRCA1/2 mutation carriers, Breast Cancer, 25,141-50, 2018

Appendices

Appendix A Review protocol

Review protocol for review question: What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

Table 4: Review protocol

ID	Field	Content
0.	PROSPERO registration number	CRD42022345284
1.	Review title	The benefits and risks of surveillance for women at increased risk of familial ovarian cancer
2.	Review question	What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?
3.	Objective	To establish the benefits and risks of surveillance for women at increased risk of familial ovarian cancer
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos • International Health Technology Assessment (INAHTA) database Searches will be restricted by: • English language

		• Human Studies The guideline committee will decide whether to re-run the searches 6 weeks before final submission of the review to retrieve further studies for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Familial ovarian cancer
6.	Population	Inclusion: Women at increased risk of familial ovarian cancer Exclusion: none

7.	Intervention	Regular (for example annual) screening for ovarian cancer, a combination of:
		• CA125 test
		• Imaging:
		  ○ transvaginal ultrasound (TVUS)
		  ○ MRI
		  ○ CT
		• Prediction rules:
		  ○ the ROCA Test
		  ○ multi-marker algorithms
		  ○ mathematical evaluation (other algorithms or techniques)

8.	Comparator	• No surveillance
		• Risk reducing treatments:
		  ○ surgery
		  ○ chemoprevention

9.	Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs

		• RCTs (test and treat studies)
		• If insufficient RCTs*:
		  ○ Quasi-randomised controlled trials
		  ○ Non-randomised controlled trials/Prospective cohort studies
		  ○ Retrospective cohort studies
		
		*Non-randomised studies will be considered for inclusion if insufficient RCT evidence is available for guideline decision making. Sufficiency will be judged taking into account factors including number/quality/sample size of RCTs, outcomes reported and availability of data from subgroups of interest.

10.	Other exclusion criteria	**Inclusion criteria**: • Full text papers • Observational studies should adjust for baseline differences between people in different intervention groups in their analyses **Exclusion criteria**: • Conference abstracts • Papers that do not include methodological details will not be included as they do not provide sufficient information to evaluate risk of bias/study quality. • Non-English language articles
11.	Context	Not applicable (no changes to scope question and no existing guidance will be updated by this review)

12.	Primary outcomes (critical outcomes)	• Quality of life
		• Survival:
		  ○ cancer specific survival
		  ○ overall survival
		  ○ recurrence free survival (surrogates: zero residual after definitive ovarian cancer treatment)

		• Ovarian cancer:
		  ○ incidence
		  ○ stage at diagnosis
		  ○ screen detected and interval related cancers
		  ○ histological type

13.	Secondary outcomes (important outcomes)	• Treatment related adverse effects and test related morbidity such as:
		  ○ anxiety
		  ○ investigation of false positive results
		• Psychological outcomes and wellbeing including:
		  ○ patient satisfaction
		  ○ acceptability and attitudes
		• Healthcare use

14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI-Reviewer and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant

		outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
15.	Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual. Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs The non-randomised study design appropriate checklist. For example, Cochrane ROBINS-I tool for non-randomised controlled trials. The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/

		Importance and imprecision of findings will be assessed against minimally important differences (MIDs). The following MIDs will be used: 0.8 and 1.25 for all relative dichotomous outcomes, for continuous outcomes any published validated MIDs, if none are available then +/- 0.5x control group SD.

17.	Analysis of sub-groups	Evidence will not be stratified
		
		Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes:
		
		• Estimated lifetime risk of ovarian cancer (for example >10%, >20%)
		• Groups identified in the equality considerations section of the scope
		  o socioeconomic and geographical factors
		  o age
		  o ethnicity
		  o disabilities
		  o people for whom English is not their first language or who have other communication needs.
		  o trans people (particularly trans men)
		  o non-binary people
		  o Type of pathogenic variant
		  o Women who have had a BSO
		  o Population based studies sub groups
		
		Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.

18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	June 2022		
22.	Anticipated completion date	March 2024		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☑

		Piloting of the study selection process	☑	☑
		Formal screening of search results against eligibility criteria	☑	☑
		Data extraction	☑	☑
		Risk of bias (quality) assessment	☑	☑
		Data analysis	☑	☑
24.	Named contact	**5a Named contact** National Institute for Health and Care Excellence (NICE) **5b Named contact e-mail** foc@nice.org.uk **5c Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)		
25.	Review team members	Senior Systematic Reviewer. Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE) Systematic Reviewer. Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)		
26.	Funding sources/sponsor	This systematic review is being completed by NICE		

27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	None
30.	Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=345284
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE
32.	Keywords	Diagnostic Screening Programs; Early Detection of Cancer; Early Diagnosis; Family; Family Health; Female; Humans; Inheritance Patterns; Ovarian Neoplasms; Mass Screening; Risk; Women

33.	Details of existing review of same topic by same authors	None
34.	Current review status	☐ Ongoing ☐ Completed but not published ☒ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35.	Additional information	None
36.	Details of final publication	www.nice.org.uk

CA125: cancer antigen 125; CT: computer tomography; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; MRI: magnetic resonance imaging; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; RoB: risk of bias; ROCA: risk of ovarian cancer algorithm; SD: standard deviation; TVUS: transvaginal ultrasound

Appendix B Literature search strategies

Literature search strategies for review question: What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

One literature search was performed for this review question and for review question L on how effective different methods of surveillance are for women at increased risk of familial ovarian cancer

Database: Ovid MEDLINE ALL

Date of last search: 23/03/2023

#	Searches
1	exp Ovarian Neoplasms/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
3	or/1-2
4	exp Breast Neoplasms/
5	exp "Neoplasms, Ductal, Lobular, and Medullary"/
6	((breast* or mammary) adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).tw,kf.
7	or/4-6
8	3 or 7
9	exp Genetic Predisposition to Disease/
10	Pedigree/
11	exp Neoplastic Syndromes, Hereditary/
12	((hereditary or inherit* or familial) adj3 (nonpolyposis or non polyposis) adj3 (colon or colorectal or bowel) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
13	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).tw,kf.
14	HNPCC.tw,kf.
15	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).tw,kf.
16	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,kf.
17	((hereditary or inherit* or familial or adenomato* or attenuated) adj3 polyp* adj3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)).tw,kf.
18	gardner* syndrome*.tw,kf.
19	(MUTYH or MYH or FAP or AFAP or APC).tw,kf.
20	((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
21	("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,kf.
22	(famil* adj2 histor* adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
23	risk factors/
24	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).tw,kf.
25	((carrier* or gene*) adj3 mutat*).tw,kf.
26	exp Genes, Tumor Suppressor/
27	exp Tumor Suppressor Proteins/
28	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).tw,kf.
29	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
30	exp Fanconi Anemia Complementation Group Proteins/
31	(Fanconi An?emia adj3 protein*).tw,kf.
32	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2).tw,kf.

#	Searches
33	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
34	Rad51 Recombinase/
35	Ataxia Telangiectasia Mutated Proteins/
36	((Ataxia telangiectasia adj1 mutated adj1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1).tw,kf.
37	Checkpoint Kinase 2/
38	(((checkpoint or check point or serine threonine) adj2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2).tw,kf.
39	Carcinoma, Small Cell/ge [Genetics]
40	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
41	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or SNF2-beta).tw,kf.
42	exp Sertoli-Leydig Cell Tumor/
43	(((Sertoli or leydig) adj3 (tumo?r* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or andr?oblastoma* or SLCT or gynandroblastoma*).tw,kf.
44	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
45	Epithelial Cell Adhesion Molecule/
46	Epithelial cell adhesion molecule*.tw,kf.
47	(EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1).tw,kf.
48	or/9-47
49	8 and 48
50	CA-125 Antigen/
51	(CA 125 or CA125).ti,ab,kf.
52	Ultrasonography/
53	(ultrasound* or ultrason* or ultra sound* or sonograph* or ultrasonograph* or echograph* or echotomograph*).ti,ab,kf.
54	(transvaginal or trans vaginal or endovaginal or endo vaginal or pelvic or cervi*).ti,ab,kf.
55	(TVUS or TVS).ti,ab.
56	Tomography, X-Ray Computed/
57	((CAT or CT or comput* or electron beam or positron emission or PET) adj2 (scan* or x ray* or xray* or tomograph*or screen*)).ti,ab,kf.
58	exp Magnetic Resonance Imaging/
59	((magnetic resonance adj2 (imag* or scan* or screen*)) or MRI).ti,ab,kf.
60	("Risk of ovarian cancer algorithm" or ROCA).ti,ab,kf.
61	algorithms/
62	algorithm*.ti,ab,kf.
63	"predictive value of tests"/ or clinical decision rules/
64	((predict* or clinical* or decision) adj2 (value* or test* or rule* or support)).ti,ab,kf.
65	exp models, statistical/
66	((math* or statistic*) adj2 (model* or evaluat* or technique* or assess* or formula* or analys?s or calculat*)).ti,ab,kf.
67	Mass Screening/ or Watchful Waiting/
68	(surveillance or watchful wait* or screen*).ti,ab,kf.
69	or/50-68
70	49 and 69
71	letter/
72	editorial/
73	news/
74	exp historical article/
75	Anecdotes as Topic/
76	comment/
77	case reports/
78	(letter or comment*).ti.
79	or/71-78

#	Searches
80	randomized controlled trial/ or random*.ti,ab.
81	79 not 80
82	animals/ not humans/
83	exp Animals, Laboratory/
84	exp Animal Experimentation/
85	exp Models, Animal/
86	exp Rodentia/
87	(rat or rats or mouse or mice or rodent*).ti.
88	or/81-87
89	70 not 88
90	limit 89 to English language
91	randomized controlled trial.pt.
92	controlled clinical trial.pt.
93	pragmatic clinical trial.pt.
94	randomi#ed.ab.
95	placebo.ab.
96	drug therapy.fs.
97	randomly.ab.
98	trial.ab.
99	groups.ab.
100	or/91-99
101	Clinical Trials as topic.sh.
102	trial.ti.
103	or/91-95,97,101-102
104	Meta-Analysis/
105	Meta-Analysis as Topic/
106	(meta analy* or metanaly* or metaanaly*).ti,ab.
107	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
108	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
109	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
110	(search* adj4 literature).ab.
111	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
112	cochrane.jw.
113	or/104-112
114	90 and (103 or 113)
115	Observational Studies as Topic/
116	Observational Study/
117	Epidemiologic Studies/
118	exp Case-Control Studies/
119	exp Cohort Studies/
120	Cross-Sectional Studies/
121	Controlled Before-After Studies/
122	Historically Controlled Study/
123	Interrupted Time Series Analysis/
124	Comparative Study.pt.
125	case control$.tw.
126	case series.tw.
127	(cohort adj (study or studies)).tw.
128	cohort analy$.tw.
129	(follow up adj (study or studies)).tw.
130	(observational adj (study or studies)).tw.
131	longitudinal.tw.

#	Searches
132	prospective.tw.
133	retrospective.tw.
134	cross sectional.tw.
135	or/115-134
136	90 and 135
137	136 not 114

Database: Ovid Embase

Date of last search: 23/03/2023

#	Searches
1	exp ovary tumor/
2	(ovar* adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
3	or/1-2
4	exp breast tumor/
5	((breast* or mammary) adj5 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)).tw,kf.
6	or/4-5
7	3 or 6
8	exp genetic predisposition/
9	pedigree/
10	exp hereditary tumor syndrome/
11	((hereditary or inherit* or familial) adj3 (nonpolyposis or non polyposis) adj3 (colon or colorectal or bowel) adj3 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
12	((lynch or Muir Torre) adj2 (syndrome* or cancer*)).tw,kf.
13	HNPCC.tw,kf.
14	(peutz* or intestin* polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* adj1 lentigino*)).tw,kf.
15	((hamartoma* or "polyps and spots" or cowden*) adj2 (syndrome* or polyp*)).tw,kf.
16	((hereditary or inherit* or familial or adenomato* or attenuated) adj3 polyp* adj3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)).tw,kf.
17	gardner* syndrome*.tw,kf.
18	(MUTYH or MYH or FAP or AFAP or APC).tw,kf.
19	((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
20	("hereditary breast and ovarian cancer" or HBOC or Li Fraumeni syndrome or SBLA or LFS).tw,kf.
21	(famil* adj2 histor* adj2 (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)).tw,kf.
22	risk factor/
23	((risk* or probabil*) adj3 (high* or increas* or factor* or rais*) adj3 (mutat* or malignan* or gene* or variant*)).tw,kf.
24	((carrier* or gene*) adj3 mutat*).tw,kf.
25	tumor suppressor gene/
26	exp tumor suppressor protein/
27	((tumo?r* or cancer* or metastas?s or growth*) adj2 (suppress* adj1 (gene* or protein*))).tw,kf.
28	(anti oncogene* or antioncogene* or onco suppressor* or oncosuppressor*).tw,kf.
29	Fanconi anemia protein/
30	(Fanconi An?emia adj3 protein*).tw,kf.
31	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2).tw,kf.
32	("breast cancer gene 1" or "breast cancer gene 2").tw,kf.
33	Rad51 protein/

#	Searches
34	ATM protein/
35	((Ataxia telangiectasia adj1 mutated adj1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1).tw,kf.
36	checkpoint kinase 2/
37	(((checkpoint or check point or serine threonine) adj2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2).tw,kf.
38	small cell carcinoma/
39	genetics/
40	38 and 39
41	(small cell adj2 (cancer* or carcinoma*) adj2 gene*).tw,kf.
42	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or SNF2-beta).tw,kf.
43	androblastoma/ or Sertoli cell tumor/ or Leydig cell tumor/
44	(((Sertoli or leydig) adj3 (tumo?r* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or andr?oblastoma* or SLCT or gynandroblastoma*).tw,kf.
45	(DICER?? or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or K12H4?8-LIKE).tw,kf.
46	epithelial cell adhesion molecule/
47	Epithelial cell adhesion molecule*.tw,kf.
48	(EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1).tw,kf.
49	or/8-37,40-48
50	7 and 49
51	CA 125 antigen/
52	(CA 125 or CA125).ti,ab,kf.
53	echography/ or transvaginal echography/
54	(ultrasound* or ultrason* or ultra sound* or sonograph* or ultrasonograph* or echograph* or echotomograph*).ti,ab,kf.
55	(transvaginal or trans vaginal or endovaginal or endo vaginal or pelvic or cervi*).ti,ab,kf.
56	(TVUS or TVS).ti,ab.
57	x-ray computed tomography/
58	((CAT or CT or comput* or electron beam or positron emission or PET) adj2 (scan* or x ray* or xray* or tomograph*or screen*)).ti,ab,kf.
59	nuclear magnetic resonance imaging/
60	((magnetic resonance adj2 (imag* or scan* or screen*)) or MRI).ti,ab,kf.
61	("Risk of ovarian cancer algorithm" or ROCA).ti,ab,kf.
62	algorithm/
63	algorithm*.ti,ab,kf.
64	predictive value/
65	clinical decision rule/
66	((predict* or clinical* or decision) adj2 (value* or test* or rule* or support)).ti,ab,kf.
67	statistical model/
68	((math* or statistic*) adj2 (model* or evaluat* or technique* or assess* or formula* or analys?s or calculat*)).ti,ab,kf.
69	screening/ or mass screening/ or watchful waiting/
70	(surveillance or watchful wait* or screen*).ti,ab,kf.
71	or/51-70
72	50 and 71
73	letter.pt. or letter/
74	note.pt.
75	editorial.pt.
76	case report/ or case study/
77	(letter or comment*).ti.
78	or/73-77
79	randomized controlled trial/ or random*.ti,ab.
80	78 not 79

#	Searches
81	animal/ not human/
82	nonhuman/
83	exp Animal Experiment/
84	exp Experimental Animal/
85	animal model/
86	exp Rodent/
87	(rat or rats or mouse or mice or rodent*).ti.
88	or/80-87
89	72 not 88
90	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
91	89 not 90
92	limit 91 to English language
93	random*.ti,ab.
94	factorial*.ti,ab.
95	(crossover* or cross over*).ti,ab.
96	((doubl* or singl*) adj blind*).ti,ab.
97	(assign* or allocat* or volunteer* or placebo*).ti,ab.
98	crossover procedure/
99	single blind procedure/
100	randomized controlled trial/
101	double blind procedure/
102	or/93-101
103	systematic review/
104	meta-analysis/
105	(meta analy* or metanaly* or metaanaly*).ti,ab.
106	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
107	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
108	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
109	(search* adj4 literature).ab.
110	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
111	((pool* or combined) adj2 (data or trials or studies or results)).ab.
112	cochrane.jw.
113	or/103-112
114	92 and (102 or 113)
115	Clinical study/
116	Case control study/
117	Family study/
118	Longitudinal study/
119	Retrospective study/
120	comparative study/
121	Prospective study/
122	Randomized controlled trials/
123	121 not 122
124	Cohort analysis/
125	cohort analy$.tw.
126	(Cohort adj (study or studies)).tw.
127	(Case control$ adj (study or studies)).tw.
128	(follow up adj (study or studies)).tw.
129	(observational adj (study or studies)).tw.
130	(epidemiologic$ adj (study or studies)).tw.
131	(cross sectional adj (study or studies)).tw.
132	case series.tw.

#	Searches
133	prospective.tw.
134	retrospective.tw.
135	or/115-120,123-134
136	92 and 135
137	136 not 114

Database: Cochrane Database of Systematic Reviews, Issue 3 of 12, March 2023 and Cochrane Central Register of Controlled Trials, Issue 3 of 12, March 2023

Date of last search: 23/03/2023

#	Searches
#1	MeSH descriptor: [Ovarian Neoplasms] explode all trees
#2	(ovar* NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#3	#1 OR #2
#4	MeSH descriptor: [Breast Neoplasms] explode all trees
#5	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#6	((breast* or mammary) NEAR/5 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)):ti,ab,kw
#7	{OR #4-#6}
#8	#3 OR #7
#9	MeSH descriptor: [Genetic Predisposition to Disease] explode all trees
#10	MeSH descriptor: [Pedigree] this term only
#11	MeSH descriptor: [Neoplastic Syndromes, Hereditary] explode all trees
#12	((hereditary or inherit* or familial) NEAR/3 (nonpolyposis or "non polyposis") NEAR/3 (colon or colorectal or bowel) NEAR/3 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#13	((lynch or "Muir Torre") NEAR/2 (syndrome* or cancer*)):ti,ab,kw
#14	HNPCC:ti,ab,kw
#15	(peutz* or intestin* NEXT polyposis or STK11 or LKB1 or PJS or hLKB1 or (perior* NEAR/1 lentigino*)):ti,ab,kw
#16	((hamartoma* or "polyps and spots" or cowden*) NEAR/2 (syndrome* or polyp*)):ti,ab,kw
#17	((hereditary or inherit* or familial or adenomato* or attenuated) NEAR/3 polyp* NEAR/3 (coli or colon or colorectal or bowel or rectum or intestin* or gastrointestin* or syndrome* or multiple)):ti,ab,kw
#18	gardner* NEXT syndrome*:ti,ab,kw
#19	(MUTYH or MYH or FAP or AFAP or APC):ti,ab,kw
#20	((familial or inherit* or heredit* or predispos* or pre NEXT dispos* or susceptib* or ancestr* or genealog* or descent) NEAR/2 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#21	("hereditary breast and ovarian cancer" or HBOC or "Li Fraumeni syndrome" or SBLA or LFS):ti,ab,kw
#22	(famil* NEAR/2 histor* NEAR/2 (cancer* or neoplas* or carcino* or malignan* or tumor* or tumour* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)):ti,ab,kw
#23	MeSH descriptor: [Risk Factors] this term only
#24	((risk* or probabil*) NEAR/3 (high* or increas* or factor* or rais*) NEAR/3 (mutat* or malignan* or gene* or variant*)):ti,ab,kw
#25	((carrier* or gene*) NEAR/3 mutat*):ti,ab,kw
#26	MeSH descriptor: [Genes, Tumor Suppressor] explode all trees
#27	MeSH descriptor: [Tumor Suppressor Proteins] explode all trees
#28	((tumor* or tumour* or cancer* or metastasis or metastases or growth*) NEAR/2 (suppress* NEAR/1 (gene* or protein*))):ti,ab,kw
#29	(anti NEXT oncogene* or antioncogene* or onco NEXT suppressor* or oncosuppressor*):ti,ab,kw
#30	MeSH descriptor: [Fanconi Anemia Complementation Group Proteins] explode all trees
#31	(("Fanconi Anemia" or "fanconi anaemia") NEAR/3 protein*):ti,ab,kw

#	Searches
#32	(BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2):ti,ab,kw
#33	("breast cancer gene 1" or "breast cancer gene 2"):ti,ab,kw
#34	MeSH descriptor: [Rad51 Recombinase] this term only
#35	MeSH descriptor: [Ataxia Telangiectasia Mutated Proteins] this term only
#36	(("Ataxia telangiectasia" NEAR/1 mutated NEAR/1 (protein* or kinase*)) or ATM or AT1 or ATA or ATC or ATD or ATDC or ATE or TEL1 or TELO1):ti,ab,kw
#37	MeSH descriptor: [Checkpoint Kinase 2] this term only
#38	(((checkpoint or "check point" or "serine threonine") NEAR/2 (protein* or kinase*)) or CHEK2 or CDS1 or CHK2 or HuCds1 or LFS2 or PP1425 or RAD53 or hCds1 or hchk2):ti,ab,kw
#39	MeSH descriptor: [Carcinoma, Small Cell] this term only and with qualifier(s): [genetics - GE]
#40	("small cell" NEAR/2 (cancer* or carcinoma*) NEAR/2 gene*):ti,ab,kw
#41	(SMARCA4 or BRG1 or CSS4 or SNF2 or SWI2 or MRD16 or RTPS2 or BAF190 or SNF2L4 or SNF2LB or hSNF2b or BAF190A or "SNF2 beta"):ti,ab,kw
#42	MeSH descriptor: [Sertoli-Leydig Cell Tumor] explode all trees
#43	(((Sertoli or leydig) NEAR/3 (tumor* or tumour* or adenoma* or cancer* or carcinoma* or neoplas* or metasta*)) or arrhenoblastoma* or androblastoma* or andreoblastoma* or SLCT or gynandroblastoma*):ti,ab,kw
#44	(DICER* or DCR1 or GLOW or MNG1 or aviD or HERNA or RMSE2 or "K12H48 LIKE"):ti,ab,kw
#45	MeSH descriptor: [Epithelial Cell Adhesion Molecule] this term only
#46	Epithelial NEXT cell NEXT adhesion NEXT molecule*:ti,ab,kw
#47	(EPCAM* or "EP CAM" or ESA or KSA or M4S1 or "MK 1" or DIAR5 or EGP* or Ly74 or gp40 or CD326 or GA733* or GA 733 or KS14 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or "MOC 31" or "Ber Ep4" or TACSTD1):ti,ab,kw
#48	{OR #9-#47}
#49	#8 AND #48
#50	MeSH descriptor: [CA-125 Antigen] this term only
#51	(CA 125 or CA125):ti,ab,kw
#52	MeSH descriptor: [Ultrasonography] this term only
#53	(ultrasound* or ultrason* or ultra NEXT sound* or sonograph* or ultrasonograph* or echograph* or echotomograph*):ti,ab,kw
#54	(transvaginal or "trans vaginal" or endovaginal or "endo vaginal" or pelvic or cervi*):ti,ab,kw
#55	(TVUS or TVS):ti,ab
#56	MeSH descriptor: [Tomography, X-Ray Computed] this term only
#57	((CAT or CT or comput* or "electron beam" or "positron emission" or PET) NEAR/2 (scan* or x NEXT ray* or xray* or tomograph*or screen*)):ti,ab,kw
#58	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#59	(("magnetic resonance" NEAR/2 (imag* or scan* or screen*)) or MRI):ti,ab,kw
#60	("Risk of ovarian cancer algorithm" or ROCA):ti,ab,kw
#61	MeSH descriptor: [Algorithms] this term only
#62	algorithm*:ti,ab,kw
#63	MeSH descriptor: [Predictive Value of Tests] this term only
#64	MeSH descriptor: [Clinical Decision Rules] this term only
#65	((predict* or clinical* or decision) NEAR/2 (value* or test* or rule* or support)):ti,ab,kw
#66	MeSH descriptor: [Models, Statistical] explode all trees
#67	((math* or statistic*) NEAR/2 (model* or evaluat* or technique* or assess* or formula* or analysis or analyses or calculat*)):ti,ab,kw
#68	MeSH descriptor: [Mass Screening] this term only
#69	MeSH descriptor: [Watchful Waiting] this term only
#70	(surveillance or watchful NEXT wait* or screen*):ti,ab,kw
#71	{OR #50-#70}
#72	#49 and #71
#73	conference:pt or (clinicaltrials or trialsearch):so
#74	#72 not #73

Database: Epistemonikos

Date of last search: 23/03/2023

#	Searches
1	(title:(((ovarian OR breast) AND (familial OR hered*) AND cancer)) OR abstract:(((ovarian OR breast) AND (familial OR hered*) AND cancer))
2	(title:((surveillance OR "watchful wait*" OR screen* OR CA-125 OR transvaginal OR ultrasound OR CT scan OR MRI OR ROCA OR prediction rule* OR clinical decision rule* OR algorithm* OR statistical model* OR math* analysis)) OR abstract:((surveillance OR "watchful wait*" OR screen* OR CA-125 OR transvaginal OR ultrasound OR CT scan OR MRI OR ROCA OR prediction rule* OR clinical decision rule* OR algorithm* OR statistical model* OR math* analysis))
3	1 AND 2

Database: INAHTA International HTA Database

Date of last search: 23/03/2023

#	Searches
36	#35 AND #14
35	#34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26 OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15
34	((surveillance or watchful wait* or screen*))[Title] OR ((surveillance or watchful wait* or screen*))[abs]
33	"Watchful Waiting"[mh]
32	"Mass Screening"[mh]
31	(((math* or statistic*) and (model* or evaluat* or technique* or assess* or formula* or analys?s or calculat*)))[Title] OR (((math* or statistic*) and (model* or evaluat* or technique* or assess* or formula* or analys?s or calculat*)))[abs]
30	"Models, Statistical"[mhe]
29	(((predict* or clinical* or decision) and (value* or test* or rule* or support)))[Title] OR (((predict* or clinical* or decision) and (value* or test* or rule* or support)))[abs]
28	"Clinical Decision Rules"[mh]
27	"Predictive Value of Tests"[mh]
26	((algorithm*))[Title] OR ((algorithm*))[abs]
25	"Algorithms"[mh]
24	(("Risk of ovarian cancer algorithm" or ROCA))[Title] OR (("Risk of ovarian cancer algorithm" or ROCA))[abs]
23	(((magnetic resonance and (imag* or scan* or screen*)) or MRI))[Title] OR (((magnetic resonance and (imag* or scan* or screen*)) or MRI))[abs]
22	"Magnetic Resonance Imaging"[mhe]
21	(((CAT or CT or comput* or electron beam or positron emission or PET) and (scan* or x ray* or xray* or tomograph*or screen*)))[Title] OR (((CAT or CT or comput* or electron beam or positron emission or PET) and (scan* or x ray* or xray* or tomograph*or screen*)))[abs]
20	"Tomography, X-Ray Computed"[mh]
19	((transvaginal or trans vaginal or endovaginal or endo vaginal or pelvic or cervi*))[Title] OR ((transvaginal or trans vaginal or endovaginal or endo vaginal or pelvic or cervi*))[abs]
18	((ultrasound* or ultrason* or ultra sound* or sonograph* or ultrasonograph* or echograph* or echotomograph*))[Title] OR ((ultrasound* or ultrason* or ultra sound* or sonograph* or ultrasonograph* or echograph* or echotomograph*))[abs]
17	"Ultrasonography"[mh]
16	((CA 125 or CA125))[Title] OR ((CA 125 or CA125))[abs]
15	"CA-125 Antigen"[mh]
14	#13 AND #8
13	#12 OR #11 OR #10 OR #9
12	((BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2 OR CHEK2 or SMARCA4 or DICER or EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1))[Title] OR ((BRCA* or IRIS or PSCP or BRCC1 or BRIP1 or BACH1 or FANC* or PNCA* or RNF53 or PPP1R53 or FAD* or FACD or GLM3 or BRCC2 or XRCC11 or TP53 or P53 or PALB2 or RAD51* or R51H3 or BROVCA* or TRAD or BARD1 or MLH1 or MSH2 or MSH6 or PMS2 OR CHEK2 or SMARCA4 or DICER or EPCAM* or EP CAM or ESA or KSA or M4S1 or MK-1 or DIAR5 or EGP??? or Ly74 or gp40 or CD326 or GA733?? or GA 733 or KS1?4 or MIC18 or TROP1 or BerEp4 or HNPCC8 or LYNCH8 or MOC-31 or Ber-Ep4 or TACSTD1))[abs]

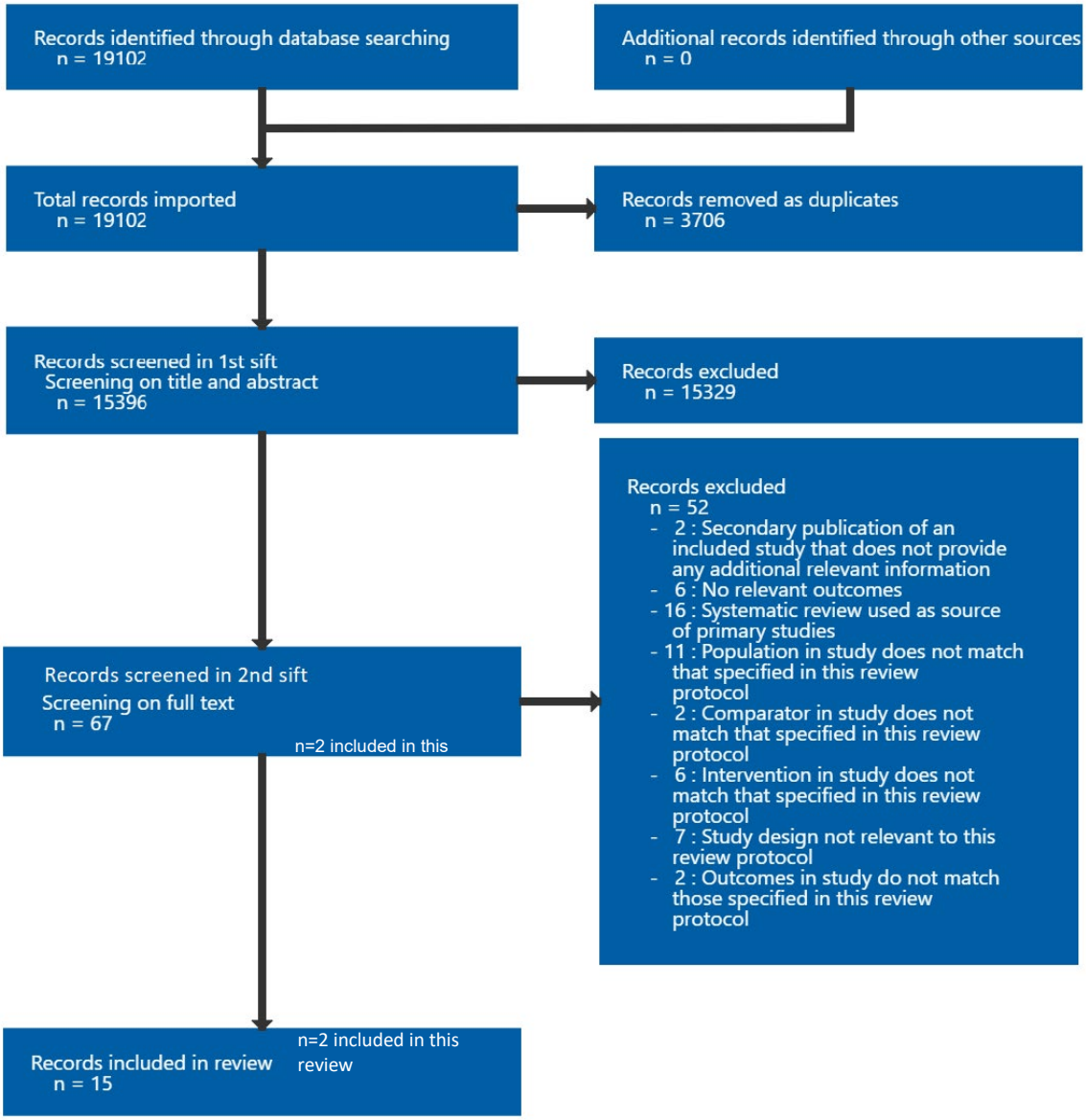
#	Searches
11	(((carrier* or gene*) and mutat*))[Title] OR (((carrier* or gene*) and mutat*))[abs]
10	((family and histor* and (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[Title] OR ((family and histor* and (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
9	(((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[Title] OR (((familial or inherit* or heredit* or predispos* or pre dispos* or susceptib* or ancestr* or genealog* or descent) AND (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
8	#7 OR #3
7	#6 OR #5 OR #4
6	(((breast* or mammary) and (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)))[Title] OR (((breast* or mammary) and (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or dcis or ductal or infiltrat* or intraductal* or lobular or medullary or metasta*)))[abs]
5	"Neoplasms, Ductal, Lobular, and Medullary"[mhe]
4	"Breast Neoplasms"[mhe]
3	#2 OR #1
2	((ovar* and (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[Title] OR ((ovar* and (cancer* or neoplas* or carcino* or malignan* or tumo?r* or adenocarcinoma* or sarcoma* or angiosarcoma* or lymphoma* or leiomyosarcoma* or metasta*)))[abs]
1	"Ovarian Neoplasms"[mhe]

Appendix C Effectiveness evidence study selection

Study selection for: What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

One literature search was performed for the review questions K and L, which is what is reflected in Figure 1. Studies included in this review were excluded from review L and studies included in review L were excluded from this review, however, these studies do not appear in the 'Records excluded' box in Figure 1, or in the respective excluded studies tables (Appendix J).

Figure 1: Study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

Lai, 2016

Bibliographic Reference	Lai, Tiffany; Kessel, Bruce; Ahn, Hyeong Jun; Terada, Keith Y; Ovarian cancer screening in menopausal females with a family history of breast or ovarian cancer; J. Gynecol. Oncol.; 2016; vol. 27 (no. 4); e41-e41

Study details

Country/ies where study was carried out	USA
Study type	Randomised controlled trial (RCT)
Study dates	November 1993 and July 2001
Inclusion criteria	Women eligible for participation were ages 55 to 74 with no previous diagnosis of lung, colorectal, or ovarian cancer. The current study used the data from a subgroup of participants who reported at least one first degree relative with breast cancer or at least one first degree relative with ovarian cancer.
Exclusion criteria	Women who had undergone previous bilateral oophorectomy were screened for lung and colorectal cancer but not for ovarian cancer, and these women were not included in this analysis. The two initial exclusion criteria of previous oophorectomy and current tamoxifen use were dropped in 1996 and 1999, respectively.
Patient characteristics	**Gender:** Women **Age, mean (SD) years:** ovarian cancer screening: 62.8 (5.4); usual medical care: 62.9 (5.5) **Ethnicity:** ovarian cancer screening: White (non-hispanic) 90.7%, Black (non-hispanic) 4.1%, Hispanic 1.5%, Asian 2.9%, Pacific Islander 0.6%, American Indian 0.3%, missing <0.1%; usual medical care: White (non-hispanic) 90.6%, Black (non-hispanic) 4.3%, Hispanic 1.6%, Asian 2.9%, Pacific Islander 0.48%, American Indian 0.21%, missing <0.1%

	Socioeconomic and geographical factors: not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported **Family history of >=2 1st degree relatives with breast/ovarian cancer (n (%)):** ovarian cancer screening 918 (8.1); usual medical care (912 (8.2)) **Family history of breast/ovarian cancer diagnosed <50 years (n (%)):** ovarian cancer screening 3520 (31.2); usual medical care 3426 (31.0) **Patients diagnosed with ovarian cancer (n (%)):** ovarian cancer screening48 (0.4); usual medical care 44 (0.4)
Intervention(s)/control	Intervention: • **Ovarian cancer screening (OCS)** A baseline pelvic ultrasound and serum CA-125, with subsequent annual pelvic ultrasound for an additional 3 years, and annual CA-125 for 5 years. Abnormal screening was determined by a CA-125 >35 U/mL, or any of the following abnormalities on pelvic ultrasound: ovarian volume >10 mL, cyst volume >10 mL, any solid area of papillary projection, or any cyst with mixed components Control: • **Usual medical care** No details reported other than that the women did not undergo cancer specific screening
Duration of follow-up	Patients were followed for a minimum of 10 years
Sources of funding	Biostatistical support was partially funded by grants from the National Institute on Minority Health and Health Disparities U54MDOO7584 and G12MDOO7601 and P20GM103466 from the National Institutes of Health.
Sample size	N=22,355

Other information	This a secondary analysis of the PLCO data by a separate group of investigators Authors assume that the majority of patients in this trial did not undergo genetic evaluation, therefore it is difficult to know the level of cancer risk for this population. The study population represents a heterogeneous group of patients with an intermediate or moderate cancer risk

PLCO: The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

Study arms

Ovarian cancer screening (N = 11293)
baseline pelvic ultrasound and serum CA125, with subsequent annual pelvic ultrasound for additional 3 years and annual CA125 for 5 years

Usual medical care (N = 11062)

Outcomes

Survival/mortality (follow-up min 10 years)

Overall survival (screening versus usual medical care) RR (95% CI; RR < 1 favours screening)	0.66 (0.47 to 0.93)
Overall mortality (screening versus usual medical care) RR (95% CI)	0.99 (0.93 to 1.06)
Ovarian cancer specific mortality (screening versus usual medical care) RR (95% CI)	0.66 (0.39 to 1.12)

CI: confidence interval; RR: risk ratio

Cancer stage at diagnosis

Outcome	Screening, N = 48	Usual medical care, N = 44
Stage I or II No of events	n = 14; % = 29	n = 8; % = 17

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(participants were aware of their assigned intervention and not clear if those delivering the interventions were also aware of participants' assigned intervention. PLCO analysis was intent-to-screen)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(participants were aware of their assigned intervention and not clear if those delivering the interventions were also aware of participants' assigned intervention).*
Overall bias and Directness	Overall Directness	Partially applicable *(Authors assume that the majority of patients in this trial did not undergo genetic evaluation, therefore it is difficult to know the level of cancer risk for*

Section	Question	Answer
		this population. Likely the study population represents a heterogeneous group of patients, some with and some without genetic mutations. As a whole, this may be construed as an intermediate or moderate risk group)

PLCO: The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

Mai, 2020

Bibliographic Reference	Mai, Phuong L; Huang, Helen Q; Wenzel, Lari B; Han, Paul K; Moser, Richard P; Rodriguez, Gustavo C; Boggess, John; Rutherford, Thomas J; Cohn, David E; Kauff, Noah D; Phillips, Kelly-Anne; Wilkinson, Kelly; Wenham, Robert M; Hamilton, Chad; Powell, Matthew A; Walker, Joan L; Greene, Mark H; Hensley, Martee L; Prospective follow-up of quality of life for participants undergoing risk-reducing salpingo-oophorectomy or ovarian cancer screening in GOG-0199: An NRG Oncology/GOG study; Gynecol. Oncol.; 2020; vol. 156 (no. 1); 131-139

Study details

Country/ies where study was carried out	USA
Study type	Prospective cohort study
Study dates	June 2003 and March 2006
Inclusion criteria	Women: • aged ≥ 30 • with no previous history of ovarian/fallopian tube/peritoneal cancer • with at least one intact ovary • if they or a close relative carried a *BRCA1/2* pathogenic variant or • if they had a personal and/or family history of BC and/or OC that conferred an increased OC risk, or ≥20% probability of carrying a *BRCA1/2* pathogenic variant based on the BRCAPRO model
Exclusion criteria	None reported

Patient characteristics	**Gender:** Women **Age, mean (SD) years:** Not reported **Age groups, range in years (%):** RRSO: 30-39=96 (17.08%), 40-49=239 (42.53%), 50-59=170 (30.25%), 60-69=47 (8.36%), >=70=10 (1.78%); ovarian cancer screening: 30-39=274 (27.13%), 40-49= 321 (31.78%), 50-59=301 (29.8%), 60-69=100 (9.9%), >=70=14 (1.39%) **Ethnicity (n):** RRSO: White = 540 (96.1%), Black = 16 (2.9%), other/not specified = 6 (1.1%); ovarian cancer screening: White = 977 (96.7%), Black = 20 (2%), other/not specified = 13 (1.3%) **Socioeconomic and geographical factors:** not reported **Disabilities:** not reported **People with communication needs (for example not English 1st language):** not reported **Non-binary people:** not reported **Self-reported mutation status (n):** RRSO: known carrier = 267 (47.5%), known non-carrier = 49 (8.7%), not tested = 193 (34.3%); ovarian cancer screening: known carrier = 160 (15.8%), known non-carrier = 196 (19.4%), not tested = 583 (57.7%)
Intervention(s)/control	Intervention: • **Ovarian cancer screening (OCS)** Participants were screened according to the ROCA Test, with CA125 measurements and ROCA Test score calculations every 3 months and annual transvaginal ultrasound (TVUS) Control: • **Risk-reducing salpingo-oophorectomy (RRSO)**

	Participants underwent the protocol-defined procedure within 90 days of enrolment. Hysterectomy was performed electively per patient and physician discretion. Participants had CA-125 measurements and the ROCA Test score calculations every 6 months during the study prospective follow-up period. Participants in the OCS cohort had the option to cross-over to the RRSO cohort post-enrolment, either electively or as prompted by screening results or clinical. Participants in the OCS arm who had RRSO during follow-up were censored at the time of RRSO, and their post-RRSO QOL assessments were excluded from the analysis.
Duration of follow-up	5 years
Sources of funding	Intramural Research Program of the US National Cancer Institute, contracts with Westat Inc., Contract #s HHSN261200109D, HHSN261200655004C and HHSN261201300003C. NCI Grants No. CA 27469 to the Gynecologic Oncology Group (GOG), NCI Community Clinical Oncology Program Grant No. CA101165, NRG Oncology (1U10 CA180822) and NRG Operations (U10CA180868). MSK Cancer Center Support Grant P30 CA008748.
Sample size	N=1780 enrolled (n=659 elected RRSO; n=1121 elected OCS) Analysis: n=562 from the RRSO group and n=1010 from the OCS group included in the analysis
Other information	Analysis: • For baseline QOL measures, the differences between the two cohorts were analysed adjusting for age, previous breast cancer (yes/no), mutation status at baseline (carrier/non-carrier/unknown), and contraceptive use (current/previous use/never). • For measures reported over time, the differences between the two cohorts were analysed by adjusting for baseline scores and age

OCS: ovarian cancer screening; QOL: quality of life; ROCA: risk of ovarian cancer algorithm; RRSO: risk-reducing salpingo-oophorectomy

Study arms

Risk-reducing salpingo-oophorectomy (RRSO) (N = 659)

Ovarian cancer screening (N = 1121)

Outcomes

Study timepoints

- Baseline
- 5 years (overall groups differences)

Risk-reducing salpingo-oophorectomy (RRSO) versus ovarian cancer screening (OCS)

Outcome	RRSO (N=562) vs OCS (N=1010), Baseline	RRSO (N=313) vs OCS (N=586), change from baseline to 5 years[a]
The Medical Outcome Study Short Form-36 (MOS SF-36): physical functioning (least square mean difference[b]) scale 0-100, higher score indicates better HRQOL Mean (95% CI)	-3.6 (-5.5 to -1.7)	0.09 (-0.97 to 1.15)
The Medical Outcome Study Short Form-36 (MOS SF-36): role functioning_physical (least square mean difference[b]) scale 0-100, higher score indicates better HRQOL Mean (95% CI)	-7.4 (-10.9 to -3.9)	-0.09 (-2.35 to 2.17)
The Medical Outcome Study Short Form-36 (MOS SF-36): role functioning_emotional (least square mean difference[b]) scale 0-100, higher score indicates better HRQOL Mean (95% CI)	-5.1 (-8.6 to -1.6)	-0.41 (-2.64 to 1.82)

Outcome	RRSO (N=562) vs OCS (N=1010), Baseline	RRSO (N=313) vs OCS (N=586), change from baseline to 5 years[a]
The Medical Outcome Study Short Form-36 (MOS SF-36): social functioning (least square mean difference[b]) scale 0-100, higher score indicates better HRQOL Mean (95% CI)	-5.6 (-7.9 to -3.2)	-0.15 (-1.81 to 1.51)
The Medical Outcome Study Short Form-36 (MOS SF-36): bodily pain (least square mean difference[b]) scale 0-100, higher score indicates better HRQOL Mean (95% CI)	-1.4 (-4 to 1.2)	-2.11 (-3.83 to -0.39)[#]
The Medical Outcome Study Short Form-36 (MOS SF-36): mental health (least square mean difference[b]) scale 0-100, higher score indicates better HRQOL Mean (95% CI)	-0.87 (-2.7 to 0.9)	-0.37 (-1.55 to 0.81)[#]
The Medical Outcome Study Short Form-36 (MOS SF-36): vitality (least square mean difference[b]) scale 0-100, higher score indicates better HRQOL Mean (95% CI)	-1.7 (-4 to 0.6)	-1.61 (--3.07 to -0.15)[#]
The Medical Outcome Study Short Form-36 (MOS SF-36): general health (least square mean difference[b]) scale 0-100, higher score indicates better HRQOL Mean (95% CI)	-0.97 (-3.1 to 1.1)	-1.28 (-2.48 to -0.08)[#]
The Impact of Events Scale (IES): overall score (least square mean difference[b]) range 0-75, lower score indicates less stress Mean (95% CI)	5.5 (4 to 7)	-4.27 (-5.07 to -3.47)[#]

Outcome	RRSO (N=562) vs OCS (N=1010), Baseline	RRSO (N=313) vs OCS (N=586), change from baseline to 5 years[a]
The Center for Epidemiology Studies Depression Scale (CES-D) (least square mean difference[b]) range 0-60, a score of >=16 indicates significant depressive symptomatology Mean (95% CI)	1.4 (0.4 to 2.4)	0.08 (-0.58 to 0.74) #
Spielberger State-Trait Anxiety Inventory (STAI): state of anxiety (least square mean difference[b]) scale 20-80, lower score indicates less anxiety Mean (95% CI)	1.9 (0.6 to 3.1)	-0.7 (-1.49 to 0.09) #
Spielberger State-Trait Anxiety Inventory (STAI): trait of anxiety (least square mean difference[b]) scale 20-80, lower score indicates less anxiety Mean (95% CI)	0.6 (-0.3 to 2)	0.32 (-0.35 to 0.99) #

CI: confidence interval; HRQOL: health-related quality of life
[a] N taken from the 5-year follow-up (received and valid questionnaire completion)
[b] least-square mean difference are from a fitted linear model with adjustment for patient's age, status of previous breast cancer (yes/no), mutation status (carrier/non-carrier/unknown), and contraceptive use (current/previous/never) at baseline; for overall effect estimates least square mean difference estimated from the fitted mixed model adjusting for baseline score, age at enrolment, assessment time, and interaction between time and groups, and adjusted for multiple testing using Sidak method
 # reported as 99% CI, converted to 95% CI by the NGA technical team

Critical appraisal ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low *(statistically significant baseline differences between study cohorts: participants in the RRSO cohort were older than those in the OCS cohort (48.6 years vs. 47.6 years, p=0.038), were more likely to report being a BRCA1/BRCA2 mutation carrier, have a personal history of breast cancer, and to not be using contraceptive at the time of enrolment; however, the*

Section	Question	Answer
		analysis for baseline measures adjusted for the above confounders and the analysis for the measures over time adjusted for baseline scores and age)
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(participants in the OCS cohort had the option to cross-over to the RRSO cohort post-enrolment, either electively or as prompted by screening results or clinical findings. However, participants in the OCS arm who had RRSO during follow-up were censored at the time of RRSO, and their post-RRSO QOL assessments were excluded from the analysis.)*
5. Bias due to missing data	Risk of bias judgement for missing data	Serious *(questionnaire response rates declined significantly over time, with ~60% of the eligible participants completing the questionnaire at 60 months. This could have been biased if participants with worse QOL disproportionately did not complete the questionnaire)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Risk of bias variation across outcomes	No variations

Section	Question	Answer
Overall bias	Directness	Directly applicable

Appendix E Forest plots

Forest plots for review question: What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

No meta-analysis was conducted for this review question and so there are no forest plots.

Appendix F GRADE tables

GRADE tables for review question: What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

Table 5: Evidence profile for comparison between ovarian cancer screening and usual medical care

Quality assessment							Number of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Screening	Usual care	Relative (95% CI)	Absolute		
Overall survival (follow-up min 10 years)												
Lai 2016	randomised trial	serious risk of bias[1]	no serious inconsistency	very serious[2]	serious[3]	none	23/11293 (0.2%)	32/11062 (0.3%)	RR 0.66 (0.47 to 0.93)	1 fewer per 1000 (from 0 fewer to 2 fewer)	VERY LOW	CRITICAL
Overall mortality (follow-up min 10 years)												
Lai 2016	randomised trial	serious risk of bias[1]	no serious inconsistency	very serious[2]	no serious imprecision	none	11293	11062	RR 0.99 (0.93 to 1.06)	Not calculable[4]	VERY LOW	CRITICAL
Ovarian cancer specific mortality (follow-up min 10 years)												
Lai 2016	randomised trial	serious risk of bias[1]	no serious inconsistency	very serious[2]	serious[3]	none	23/11293 (0.2%)	32/11062 (0.3%)	RR 0.66 (0.39 to 1.12)	1 fewer per 1000 (from 2 fewer to 0 fewer)	VERY LOW	CRITICAL
Ovarian cancer stage at diagnosis: proportion of ovarian cancers that were stage I or II at diagnosis												
Lai 2016	randomised trial	serious risk of bias[1]	no serious inconsistency	very serious[2]	very serious[5]	none	14/48 (29%)	8/44 (17%)	RR 1.60 (0.75 to 3.45)	109 more per 1000 (from 45 fewer to 445 more)	VERY LOW	CRITICAL

CI: confidence interval; MID: minimal important difference; RR: risk ratio
1 Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
2 The majority of patients in this trial did not undergo genetic evaluation, therefore it is difficult to know the level of cancer risk for this population. Likely the study population represents a heterogeneous group of patients, some with and some without genetic mutations (intermediate or moderate risk group)
3 95% CI crosses 1 MID

4 Event rates not reported
5 95% CI crosses 2 MIDs

Table 6: Evidence profile for comparison between risk-reducing salpingo-oophorectomy and ovarian cancer screening

Quality assessment							Number of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RRSO[1]	Screening[1]	Relative (95% CI)	Absolute (95% CI)[2]		
Quality of life: Physical sub-scale of MOS SF-36 [scale 0-100, higher score indicates better HRQOL], change from baseline to 5 years follow-up												
Mai 2020	prospective cohort	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	586	NA	MD 0.09 (-0.97 to 1.15)	MODERATE	CRITICAL
Quality of life: Role functioning physical sub-scale of MOS SF-36 [scale 0-100, higher score indicates better HRQOL], change from baseline to 5 years follow-up												
Mai 2020	prospective cohort	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	586	NA	MD -0.09 (-2.35 to 2.17)	MODERATE	CRITICAL
Quality of life: Role functioning emotional sub-scale of MOS SF-36 [scale 0-100, higher score indicates better HRQOL], change from baseline to 5 years follow-up												
Mai 2020	prospective cohort	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	586	NA	MD -0.41 (-2.64 to 1.82)	MODERATE	CRITICAL
Quality of life: Social functioning sub-scale of MOS SF-36 [scale 0-100, higher score indicates better HRQOL], change from baseline to 5 years follow-up												
Mai 2020	prospective cohort	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	586	NA	MD -0.15 (-1.81 to 1.51)	MODERATE	CRITICAL
Quality of life: Bodily pain sub-scale of MOS SF-36 [scale 0-100, higher score indicates better HRQOL], change from baseline to 5 years follow-up												
Mai 2020	prospective cohort	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	586	NA	MD -2.11 (-3.83 to -0.39)	MODERATE	CRITICAL

Quality assessment							Number of participants		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RRSO[1]	Screening[1]	Relative (95% CI)	Absolute (95% CI)[2]		
Quality of life: Mental health sub-scale of MOS SF-36 [scale 0-100, higher score indicates better HRQOL], change from baseline to 5 years follow-up												
Mai 2020	prospective cohort	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	586	NA	MD -0.37 (-1.55 to 0.81)	MODERATE	CRITICAL
Quality of life: Vitality sub-scale of MOS SF-36 [scale 0-100, higher score indicates better HRQOL], change from baseline to 5 years follow-up												
Mai 2020	prospective cohort	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	586	NA	MD -1.61 (-3.07 to -0.15)	MODERATE	CRITICAL
Quality of life: General health sub-scale of MOS SF-36 [scale 0-100, higher score indicates better HRQOL], change from baseline to 5 years follow-up												
Mai 2020	prospective cohort	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	586	NA	MD -1.28 (-2.48 to -0.08)	MODERATE	CRITICAL
Quality of life: The Impact of Events Scale (IES): overall score, [range 0-75, lower score indicates less stress], change from baseline to 5 years follow-up												
Mai 2020	prospective cohort	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	586	NA	MD -4.27 (-5.07 to -3.47)	MODERATE	CRITICAL
Psychological outcomes: The Center for Epidemiology Studies Depression Scale (CES-D), baseline [range 0-60, a score of >=16 indicates significant depressive symptomatology], change from baseline to 5 years follow-up												
Mai 2020	prospective cohort	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	586	NA	MD 0.08 (-0.58 to 0.74)	MODERATE	CRITICAL
Anxiety: State of anxiety, Spielberger State-Trait Anxiety Inventory (STAI), [scale 20-80, lower score indicates less anxiety], change from baseline to 5 years follow-up												

Quality assessment							Number of participants		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**RRSO[1]**	**Screening[1]**	**Relative (95% CI)**	**Absolute (95% CI)[2]**		
Mai 2020	prospective cohort	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	586	NA	MD -0.7 (-1.49 to 0.09)	MODERATE	IMPORTANT
Anxiety: trait of anxiety, Spielberger State-Trait Anxiety Inventory (STAI), [scale 20-80, lower score indicates less anxiety], overall group differences reported between baseline and 5 years follow-up												
Mai 2020	prospective cohort	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	586	NA	MD 0.32 (-0.35 to 0.99)	MODERATE	IMPORTANT

CI: confidence interval; HRQOL: health-related quality of life; MD: mean difference; MID: minimal important difference; MOS SF-36: The Medical Outcome Study Short Form-36; NA: not applicable; RRSO: risk-reducing salpingo-oophorectomy
1 No usable raw data reported therefore not possible to calculate mean differences; the least square mean differences (with an adjustment for some differences between the groups) were reported therefore the differences between the RRSO and screening groups here were reported in the same way as in the publication (that is RRSO vs screening).
2 Least squares mean, 95% CI was calculated from the reported 99% CI for the overall follow-up; importance and imprecision of findings assessed against MIDs for continuous outcomes as there are no MIDs in ovarian cancer or breast cancer populations published.
3 Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I

Appendix G Economic evidence study selection

Study selection for: What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

One global search was undertaken – please see Supplement 2 for details on study selection.

Appendix H Economic evidence tables

Economic evidence tables for review question: What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

Table 7: Economic evidence tables for surveillance for people with a confirmed *BRCA* genetic mutation

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
Bommer 2022 Switzerland Cost-utility analysis Source of funding: University of Zurich	Intervention -Intensified surveillance, IS (age-related imaging procedures and gynaecological consultations) Comparators -Bilateral mastectomy (PBM) -Bilateral salpingo-oophorectomy (PBSO) PBM plus PBSO -Chemoprevention with Tamoxifen (CP)	A cohort of female *BRCA1* or *BRCA2* mutation carriers aged 40 years who had no history of breast or ovarian cancer Modelling study (Markov) Source of baseline data: Various sources, mainly cohort studies Source of effectiveness data: Cohort studies and RCT for chemotherapy Source of cost data: Various published sources supplemented with authors' assumptions Source of unit cost data: National (Swiss diagnosis-related group	Costs: -Surveillance and cancer follow-up (clinical consultations, mammography, magnetic resonance imaging (MRI), computerized tomography (CT) scans, oncologic consultation, blood sampling and analysis, ultrasound, osteodensitometry), -PBM with autologous breast reconstruction or implant-based breast reconstruction, PBSO, cancer surgery (BM or BSO, hysterectomy, debulking in abdomen, pelvis), breast reshaping, implant replacement, -Radiation therapy, -Palliative care, -Chemotherapy-associated costs (hospital, production tax, material costs, before each cycle [blood sampling,	ICERs: -IS dominated by all options (lower costs and QALY gain) -For both *BRCA1* and *BRCA2*: PBM & PBSO dominant Probability of being cost-effective: At a willingness-to-pay (WTP) from €0 to €100,000/QALY gained -PBM & PBSO: 100% (for both *BRCA1* and BRCA2) Subgroup analysis: NR Sensitivity analysis: Changes in ovarian cancer (OC) incidence after primary breast cancer (BC), PBSO costs, hazard ratio of PBSO, PBM costs with implant reconstruction, costs of	Perspective: Healthcare payer Currency: Euro (€) Cost year: Likely 2019 Time horizon: 60 years (lifetime) Discounting: 3% for costs and QALYs Applicability: Partially Limitations: Minor

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		(DRG) system, Tarmed national tariff system, Swiss statutory health insurance)	laboratory and chemotherapy choice by oncologist], chemotherapy-related medications (antiemetics, hematopoietic growth factor, bisphosphonates, paclitaxel) Mean lifetime cost per participant: *BRCA1* IS: €141,293 CP: €136,957 PBM: €115,802 PBSO: €112,814 PBM & PBSO: €76,639 *BRCA2* IS: €102,245 CP: €97,091 PBM: €78,478 PBSO: €70,562 PBM & PBSO: €60,770 The primary measure of outcome: QALYs (with utility weights from various published sources, some were based on EQ-5D)	implant replacement, utility values of IS and CP have the most effects on the ICERs. However, the conclusions were unchanged.	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			Mean lifetime QALYs per participant: *BRCA1* IS: 14.48 CP: 15.24 PBM: 17.28 PBSO: 16.79 PBM & PBSO: 19.24 *BRCA2* IS: 15.52 CP: 16.85 PBM: 17.58 PBSO: 19.24 PBM & PBSO: 19.85		
Muller 2018 Germany Cost-utility analysis Source of funding: Federal Ministry of Education and Research	Intervention -Intensified surveillance, IS (half-yearly palpation and ultrasound, yearly mammography, and breast magnetic resonance imaging) Comparators -Bilateral mastectomy (PBM) - Bilateral salpingo-oophorectomy (PBSO)	A cohort of 30-year-old female *BRCA* mutation carriers aged 30 years who had no history of breast or ovarian cancer Modelling study (Markov) Source of baseline data: A cohort study Source of effectiveness data: Cohort studies	Costs: -Ongoing high-risk screening/surveillance -Surgical options (PBM, PBSO, PBM plus PBSO) therapeutic BM, breast-conserving surgery, therapeutic BSO) -BC medication (chemotherapy, endocrine therapy, neutropenic sepsis, Neulasta (pegfilgrastim), antiemetics, bisphosphonates) -Other BC treatments (adjuvant radiotherapy, local surgeries, psychological treatment in	IS dominated by all surgical options (greatest cost and lowest QALY gain) PBM + PBSO at age 30: dominant Probability of being cost-effective: At willingness-to-pay (WTP) of €0/QALY gained PBM + PBSO at age 30: 57% PBM + PBSO at age 40: 33% PBSO: 10%	Perspective: Healthcare payer Currency: Euro (€) Cost year: NR; likely 2016 Time horizon: 75 years (lifetime) Discounting: 3% for costs and QALYs Applicability: Partially Limitations: Minor

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
	-Mastectomy + oophorectomy (PBM+PBSO) at age 40 -PBM+PBSO at age 30	Source of cost data: Various published sources Source of unit cost data: Unclear, some local (prophylactic and therapeutic surgical costs from actuarial data from the University Hospital of Cologne)	case of cancer diagnosis), lymphatic drainage/physiotherapy (BC) -OC medication -Palliative care Mean lifetime cost per participant: IS: €45,480 PBM + PBSO at age 30: €29,434 PBM + PBSO at age 40: €30,810 PBSO: €34,802 PBM: €37,307 The primary measure of outcome: QALYs (utility weights from various published sources) Mean lifetime QALYs per participant: IS: 14.96 PBM + PBSO at age 30: 17.66 PBM + PBSO at age 40: 17.28 PBSO: 16.71 PBM: 16.27	PBM: 0% IS: 0% At WTP of €50,000/QALY gained PBM + PBSO at age 30: 86% PBM + PBSO at age 40: 14% PBSO: 0% PBM: 0% IS: 0% Subgroup analysis: NR Sensitivity analysis: -The results were robust, including changes in cancer incidence, mortality, utility assumptions, the efficacy of surgical options, the discount rate, differentiating between 'ovarian cancer' (<stage 4) and 'recurrent ovarian cancer' (stage 4) states - Only in case of a lower OC incidence or both OC and BC incidence, does PBM + PBSO at age 40 result in lower costs, but PBS + PBSO at age 30 remains the cost-effective option -Assuming that the utility after prophylactic surgery	

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
				increased to that of a healthy woman within a period of 25 years (base-case: 5 years), the ICER of PBM + PBSO at age 40 (vs PBM + PBSO at age 30): €6,900/QALY	
Philpott 2023 UK Cost-utility analysis Source of funding: Abcodia Ltd and North Central London Cancer Alliance. Multiple authors have competing interests with various private companies.	Intervention 4-monthly surveillance with the ROCA Test, which uses longitudinal serum CA125 results, age, menopausal status, and lifetime risk category Comparators No surveillance (control women were assumed to have the option of undergoing risk-reducing salpingo-oophorectomy, remaining disease-free or developing ovarian cancer and entering the associated therapy)	A hypothetical cohort of *BRCA1/2*-heterozygotes offered surveillance starting at the age of 35 years Modelling study (Markov) Source of baseline data: Prospective multicentre UK cohort screening study, N = 4,348 Source of effectiveness data: Prospective multicentre UK cohort screening study, N = 875 Source of cost data: Prospective UK cohort screening study (N = 875) and other published literature Source of unit cost data: National sources (NHS	Costs (type): the ROCA Test, surveillance visits, blood tests, clinic visits, surgery and follow-up clinical assessment, ovarian cancer chemotherapy, including maintenance therapy Mean lifetime cost per participant: Intervention: £202,337 Control: £220,677 Difference: -£18,340 The primary measure of outcome: QALYs (EQ-5D data for people with recurrent ovarian cancer) Mean lifetime QALYs per participant: Intervention: 31.6641 Control: 31.4291 Difference: 0.179	ICERs: Surveillance dominant Probability of being cost-effective: NR Subgroup analysis: NR Sensitivity analysis: - At the ROCA Test unit cost of £585 (base case £150), the ICER of surveillance was £987/QALY gained - Surveillance remained dominant when varying surveillance duration from 50-80 years - Only at the early-stage (stages 1/2) cancer detection rate set at 11.5% (base case: 33.3%) the ICER of surveillance increased to £971/QALY gained	Perspective: UK NHS Currency: UK£ Cost year: Unclear (sources with dates ranging from 2019-21) Time horizon: Lifetime Discounting: 1.5% for costs and outcomes Applicability: Directly (UK study, QALYs) Limitations: Minor

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
		Reference Costs, British National Formulary, PSSRU, the ROCA Test from manufacturer)			
Yamauchi 2018 Japan Cost-utility analysis Source of funding: a Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labour and Welfare	Intervention Intensified surveillance, IS from age 35 -Breast cancer (once a year mammogram (MMG), magnetic resonance imaging (MRI), and examination) -Ovarian cancer (twice a year blood test, chemistry, transvaginal ultrasound) Comparators -Preventative mastectomy (PBM) at age 35 + preventative salpingo-oophorectomy (PBSO) at age 45 - IS from age 35, PBSO at age 45 - PBM at age 35	A cohort of female *BRCA1* and *BRCA2* mutation carriers aged 35 years who had no cancer diagnosis at baseline Modelling study (Markov) Source of baseline data: A cohort study Source of effectiveness data: Various published studies including case-control and cohort studies Source of cost data: Receipts, fees and medicine charges in Japan at St. Luke's International Hospital and Keio University Hospital Source of unit cost data: Unclear	Costs: Risk-reducing surgery, breast / ovarian cancer operation, breast / ovarian cancer adjuvant chemotherapy, ovarian and breast cancer screening (mammogram, magnetic resonance imaging, examination, blood test, chemistry, transvaginal ultrasound, computerized tomography scan), adverse event management, progression (chemotherapy, scans, palliative care) Mean cost per participant over 35 years: *BRCA1* IS from age 35: ¥6,119,067 PBM at age 35, PBSO at age 45: ¥5,333,801 IS from age 35, PBSO at age 45: ¥5,803,532 PBM at age 35: ¥6,185,091 *BRCA2*	IS was not cost-effective for both *BRCA1* and *BRCA2* carriers For *BRCA1*: PBM at age 35, PBSO at age 45 dominant (lower cost, and greatest QALY gain) For *BRCA2*: PBM at age 35 dominant Probability of being cost-effective: NR Subgroup analysis: NR Sensitivity analysis: Findings robust to model inputs, including probabilities and costs. However, using lower values for some utilities for preventative surgical procedures resulted in changes in results that favoured IS, but results were not reported.	Perspective: Healthcare payer Currency: Japanese Yen (¥) Cost year: 2016 Time horizon: 35 years Discounting: 2% Applicability: Partially Limitations: Potentially serious

Study country and type	Intervention and comparator	Study population, design and data sources	Costs and outcomes (descriptions and values)	Results	Comments
			IS from age 35: ¥4,719,326 PBM at age 35: ¥3,744,163 PBM at age 35, PBSO at age 45: ¥4,245,410 IS from age 35, PBSO at age 45: ¥5,329,849 The primary measure of outcome: QALYs (utility weights from various published sources) Mean QALYs per participant over 35 years: *BRCA1* IS from age 35: 16.57 PBM at age 35, PBSO at age 45: 18.06 IS from age 35, PBSO at age 45: 18.00 PBM at age 35: 17.61 *BRCA2* IS from age 35: 19.29 PBM at age 35: 21.11 PBM at age 35, PBSO at age 45: 20.20 IS from age 35, PBSO at age 45: 19.94		

Insert abbreviations: BC: Breast cancer; CP: Chemoprevention; CT: Computed tomography; DRG: Diagnosis related group; EQ-5D: EuroQol 5 dimensions; ICER: Incremental cost-effectiveness ratio; IS: Intensified surveillance; MMG: Mammogram; MRI: Magnetic resonance imaging; NR: Not reported; OC: Ovarian cancer; PBM: Preventative bilateral mastectomy; PBSO: Preventative bilateral salpingo-oophorectomy; QALY: Quality-adjusted life year; RCT: Randomised controlled trial.

Appendix I Economic model

Economic model for review question: What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

Excluded effectiveness/diagnostic studies

One literature search was performed for the review questions K and L. Studies included in this review were excluded from review L and studies included in review L were excluded from this review however, these studies do not appear in the 'Records excluded' box in Figure 1, or in the respective excluded studies tables below.

Table 8: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Andersen, M Robyn, Drescher, Charles W, Zheng, Yingye et al. (2007) Changes in cancer worry associated with participation in ovarian cancer screening. Psycho-oncology 16(9): 814-20	- Population in study does not match that specified in this review protocol W*omen not at increased risk of familial ovarian cancer*
Andersen, M Robyn, Karlan, Beth Y, Drescher, Charles W et al. (2019) False-positive screening events and worry influence decisions about surgery among high-risk women. Health psychology: official journal of the Division of Health Psychology, American Psychological Association 38(1): 43-52	- Outcomes in study do not match those specified in this review protocol*Secondary analysis of Karlan 2014*
Auranen, Annika and Joutsiniemi, Titta (2011) A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families. Acta obstetricia et gynecologica Scandinavica 90(5): 437-44	- Systematic review used as source of primary studies
Belkic, K.L., Cohen, M., Marquez, M. et al. (2010) Screening of high-risk groups for breast and ovarian cancer in Europe: A focus on the Jewish population. Oncology Reviews 4(4): 233-267	- Systematic review used as source of primary studies
Bermejo-Perez, M J; Marquez-Calderon, S; Llanos-Mendez, A (2007) Effectiveness of preventive interventions in BRCA1/2 gene mutation carriers: a systematic review. International journal of cancer 121(2): 225-31	- Systematic review used as source of primary studies
Bermejo-Perez, M J; Marquez-Calderon, S; Llanos-Mendez, A (2008) Cancer surveillance based on imaging techniques in carriers of BRCA1/2 gene mutations: a systematic review. The British journal of radiology 81(963): 172-9	- Systematic review used as source of primary studies
Blyuss, Oleg, Burnell, Matthew, Ryan, Andy et al. (2018) Comparison of Longitudinal CA125 Algorithms as a First-Line Screen for Ovarian Cancer in the General Population. Clinical cancer research : an official journal of the American Association for Cancer Research 24(19): 4726-4733	- Population in study does not match that specified in this review protocol *Women with increased risk of familial ovarian cancer were excluded*
Bourne, T H, Campbell, S, Reynolds, K et al. (1994) The potential role of serum CA 125 in an ultrasound-based screening program for familial ovarian cancer. Gynecologic oncology 52(3): 379-85	- Outcomes in study do not match those specified in this review protocol *Outcomes reported for screening group only*
Buys, Saundra S, Partridge, Edward, Black, Amanda et al. (2011) Effect of screening on ovarian cancer mortality: the	- Population in study does not match that specified in this review protocol

Study	Reason for exclusion
Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA 305(22): 2295-2303	*Results not reported separately for the subgroup s of women with a family or personal history of ovarian cancer. Trialists contacted to ask for this subgroup data*
Debniak, Tadeusz, Gromowski, Tomasz, Scott, Rodney J et al. (2015) Management of ovarian and endometrial cancers in women belonging to HNPCC carrier families: review of the literature and results of cancer risk assessment in Polish HNPCC families. Hereditary cancer in clinical practice 13(1): 3	- Intervention in study does not match that specified in this review protocol *No details of surveillance protocol used for ovarian cancer*
Drescher, Charles W, Nelson, Judy, Peacock, Sue et al. (2004) Compliance of average- and intermediate-risk women to semiannual ovarian cancer screening. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 13(4): 600-6	- Outcomes in study do not match those specified in this review protocol *Compliance with screening only*
Eikenboom, E.L., Van Doorn, H.C., Dinjens, W.N.M. et al. (2021) Gynecological surveillance and surgery outcomes in dutch lynch syndrome carriers. Cancers 13(3): 1-16	- Intervention in study does not match that specified in this review protocol *Study assesses gynaecological tumours and gynaecological management in Lynch Syndrome carriers*
Eleje, George U, Eke, Ahizechukwu C, Ezebialu, Ifeanyichukwu U et al. (2018) Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations. The Cochrane database of systematic reviews 8: cd012464	- Intervention in study does not match that specified in this review protocol *RRSO is compared to general surveillance or non-RRSO - but no details of surveillance protocols are given*
Fatouros, Michael; Baltoyiannis, Georgios; Roukos, Dimitrios H (2008) The predominant role of surgery in the prevention and new trends in the surgical treatment of women with BRCA1/2 mutations. Annals of surgical oncology 15(1): 21-33	- Systematic review used as source of primary studies
Fries, Melissa H, Hailey, B Jo, Flanagan, Judith et al. (2004) Outcome of five years of accelerated surveillance in patients at high risk for inherited breast/ovarian cancer: report of a phase II trial. Military medicine 169(6): 411-6	- Comparator in study does not match that specified in this review protocol *Does not compare surveillance to an alternative strategy*
Fry, A, Busby-Earle, C, Rush, R et al. (2001) Prophylactic oophorectomy versus screening: psychosocial outcomes in women at increased risk of ovarian cancer. Psycho-oncology 10(3): 231-41	- Study design does not match that specified in this review protocol *Non-randomised study, does not adjust for confounders in the analysis*
Gentry-Maharaj, A., Blyuss, O., Ryan, A. et al. (2020) Multi-marker longitudinal algorithms incorporating HE4 and CA125 in ovarian cancer screening of postmenopausal women. Cancers 12(7): 1-12	- Population in study does not match that specified in this review protocol *Women with increased risk of familial ovarian cancer were excluded*
Gentry-Maharaj, A, Sharma, A, Burnell, M et al. (2013) Acceptance of transvaginal sonography by postmenopausal women participating in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 41(1): 73-9	- Population in study does not match that specified in this review protocol *Women with increased risk of familial ovarian cancer were excluded*

Study	Reason for exclusion
Gopie, Jessica P; Vasen, Hans F A; Tibben, Aad (2012) Surveillance for hereditary cancer: does the benefit outweigh the psychological burden?--A systematic review. Critical reviews in oncology/hematology 83(3): 329-40	- Systematic review used as source of primary studies
Grandi, Giovanni, Fiocchi, Federica, Cortesi, Laura et al. (2021) The challenging screen detection of ovarian cancer in BRCA mutation carriers adhering to a 6-month follow-up program: results from a 6-years surveillance. Menopause (New York, N.Y.) 29(1): 63-72	- Secondary publication of an included study that does not provide any additional relevant information *See Cortesi 2017*
Gronwald, Jacek, Lubinski, Jan, Huzarski, Tomasz et al. (2019) A comparison of ovarian cancer mortality in women with BRCA1 mutations undergoing annual ultrasound screening or preventive oophorectomy. Gynecologic oncology 155(2): 270-274	- Study design does not match that specified in this review protocol *Comparisons between groups not adjusted for baseline differences*
Haque, Reina, Skates, Steven J, Armstrong, Mary Anne et al. (2020) Feasibility, patient compliance and acceptability of ovarian cancer surveillance using two serum biomarkers and Risk of Ovarian Cancer Algorithm compared to standard ultrasound and CA 125 among women with BRCA mutations. Gynecologic oncology 157(2): 521-528	- Secondary publication of an included study that does not provide any additional relevant information *See Lentz 2020*
Henderson, J.T.; Webber, E.M.; Sawaya, G.F. (2018) Screening for ovarian cancer updated evidence report and systematic review for the US preventive services task force. JAMA - Journal of the American Medical Association 319(6): 595-606	- Systematic review used as source of primary studies
Jacobs, Ian J, Menon, Usha, Ryan, Andy et al. (2016) Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet (London, England) 387(10022): 945-956	- Population in study does not match that specified in this review protocol *Women with increased risk of familial ovarian cancer were excluded*
Kobayashi, H, Yamada, Y, Sado, T et al. (2008) A randomized study of screening for ovarian cancer: a multicenter study in Japan. Int. J. Gynecol. Cancer 18(3): 414-420	- Population in study does not match that specified in this review protocol *Participants not at increased risk of familial ovarian cancer. No subgroup analysis of increased risk groups*
Lacey Jr., J.V., Greene, M.H., Buys, S.S. et al. (2006) Ovarian cancer screening in women with a family history of breast or ovarian cancer. Obstetrics and Gynecology 108(5): 1176-1184	- Outcomes in study do not match those specified in this review protocol *Insufficient data to calculate diagnostic outcomes.*
Laframboise, Stephane, Nedelcu, R, Murphy, J et al. (2002) Use of CA-125 and ultrasound in high-risk women. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society 12(1): 86-91	Outcomes in study do not match those specified in this review protocol *Insufficient data to calculate diagnostic outcomes*
Li, Jiaxin, Jia, Ziqi, Zhang, Menglu et al. (2021) Cost-Effectiveness Analysis of Imaging Modalities for Breast Cancer Surveillance Among BRCA1/2 Mutation Carriers: A Systematic Review. Frontiers in oncology 11: 763161	- Systematic review used as source of primary studies
Lim, Natalie, Hickey, Martha, Young, Graeme P et al. (2022) Screening and risk reducing surgery for endometrial or ovarian cancers in Lynch syndrome: a systematic review. International journal of gynecological cancer: official journal of the International Gynecological Cancer Society 32(5): 646-655	- Outcomes in study do not match those specified in this review protocol *Insufficient data to calculate diagnostic outcomes.*

Study	Reason for exclusion
Lockwood, S. and Ritzert, B. (2013) Cost-effectiveness of serum CA125 compared to transvaginal ultrasound as a screening test for ovarian cancer: A systematic review protocol. JBI Library of Systematic Reviews 11(10): 89-106	- Study design does not match that specified in this review protocol *Systematic review protocol*
Mallen, Adrianne, Soong, T Rinda, Townsend, Mary K et al. (2018) Surgical prevention strategies in ovarian cancer. Gynecologic oncology 151(1): 166-175	- Systematic review used as source of primary studies
Marchetti, C., De Felice, F., Perniola, G. et al. (2018) Screening program in ovarian cancer: A logical step in clinical management? A meta-analysis. Current Problems in Cancer 42(2): 235-240	- Systematic review used as source of primary studies
Menon, Usha, Gentry-Maharaj, Aleksandra, Burnell, Matthew et al. (2021) Ovarian cancer population screening and mortality after long-term follow-up in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet (London, England) 397(10290): 2182-2193	- Population in study does not match that specified in this review protocol *Women with increased risk of familial ovarian cancer were excluded*
Menon, Usha, Gentry-Maharaj, Aleksandra, Hallett, Rachel et al. (2009) Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). The Lancet. Oncology 10(4): 327-40	- Population in study does not match that specified in this review protocol *Women with increased risk of familial ovarian cancer were excluded*
Menon, Usha, Ryan, Andy, Kalsi, Jatinderpal et al. (2015) Risk Algorithm Using Serial Biomarker Measurements Doubles the Number of Screen-Detected Cancers Compared With a Single-Threshold Rule in the United Kingdom Collaborative Trial of Ovarian Cancer Screening. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33(18): 2062-71	- Population in study does not match that specified in this review protocol *Women at increased risk of familial ovarian cancer were excluded*
Moller, Pal, Seppala, Toni, Bernstein, Inge et al. (2017) Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut 66(3): 464-472	- Intervention in study does not match that specified in this review protocol *Colonoscopic surveillance*
Pinsky, Paul F, Yu, Kelly, Kramer, Barnett S et al. (2016) Extended mortality results for ovarian cancer screening in the PLCO trial with median 15years follow-up. Gynecol. Oncol. 143(2): 270-275	- Population in study does not match that specified in this review protocol *Results not reported separately for the subgroup of women with a family history of breast or ovarian cancer*
Ramamurthy, C.; Chertock, Y.; Hall, M.J. (2017) Randomized Controlled Trials in Hereditary Cancer Syndromes. Surgical Oncology Clinics of North America 26(4): 729-750	- Systematic review used as source of primary studies
Reade, C.J., Riva, J.J., Busse, J.W. et al. (2013) Risks and benefits of screening asymptomatic women for ovarian cancer: A systematic review and meta-analysis. Gynecologic Oncology 130(3): 674-681	- Systematic review used as source of primary studies
Renaud, M.-C. and Le, T. (2018) No. 291-Epidemiology and Investigations forSuspected Endometrial Cancer. Journal of Obstetrics and Gynaecology Canada 40(9): e703-e711	- Study design does not match that specified in this review protocol *Clinical practice guideline*
Salhab, Mohamed; Bismohun, Selina; Mokbel, Kefah (2010) Risk-reducing strategies for women carrying BRCA1/2 mutations with a focus on prophylactic surgery. BMC women's health 10: 28	- Systematic review used as source of primary studies

Study	Reason for exclusion
Schmeler, KM, Sun, CC, Bodurka, DC et al. (2006) Prophylactic bilateral salpingo-oophorectomy compared with surveillance in women with BRCA mutations. Obstetrics and gynecology 108(3pt1): 515-520	- Study design does not match that specified in this review protocol *Analysis does not adjust for baseline differences between groups*
Sherman, Mark E, Piedmonte, Marion, Mai, Phuong L et al. (2014) Pathologic findings at risk-reducing salpingo-oophorectomy: primary results from Gynecologic Oncology Group Trial GOG-0199. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 32(29): 3275-83	- Comparator in study does not match that specified in this review protocol *Outcomes reported for RRSO group only*
Sroczynski, Gaby, Gogollari, Artemisa, Kuehne, Felicitas et al. (2020) A Systematic Review on Cost-effectiveness Studies Evaluating Ovarian Cancer Early Detection and Prevention Strategies. Cancer prevention research (Philadelphia, Pa.) 13(5): 429-442	- Systematic review used as source of primary studies
Stewart, M.E., Knisely, A.T., Sullivan, M.W. et al. (2019) Evaluation of screening and risk-reducing surgery for women followed in a high-risk breast/ovarian cancer clinic: it is all about the tubes in BRCA mutation carriers. Gynecologic Oncology Reports 28: 18-22	- Intervention in study does not match that specified in this review protocol *Outcomes reported for RRSO group only*
Tailor, A, Bourne, TH, Campbell, S et al. (2003) Results from an ultrasound-based familial ovarian cancer screening clinic: a 10-year observational study. Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology 21(4): 378-85	- Study design does not match that specified in this review protocol *Outcomes reported for screening group only*
Tschernichovsky, Roi and Goodman, Annekathryn (2017) Risk-Reducing Strategies for Ovarian Cancer in BRCA Mutation Carriers: A Balancing Act. The oncologist 22(4): 450-459	- Systematic review used as source of primary studies
Tzortzatos, Gerasimos, Andersson, Emil, Soller, Maria et al. (2015) The gynecological surveillance of women with Lynch syndrome in Sweden. Gynecologic oncology 138(3): 717-22	- Intervention in study does not match that specified in this review protocol *Outcomes reported for screening group only*
van Driel, Catheleine M G, de Bock, Geertruida H, Arts, Henriette J G et al. (2015) Stopping ovarian cancer screening in BRCA1/2 mutation carriers: effects on risk management decisions & outcome of risk-reducing salpingo-oophorectomy specimens. Maturitas 80(3): 318-22	- Outcomes in study do not match those specified in this review protocol *Interval cancers (not detected by screening) not reported*
Vasen, H F A, Tesfay, E, Boonstra, H et al. (2005) Early detection of breast and ovarian cancer in families with BRCA mutations. European journal of cancer (Oxford, England : 1990) 41(4): 549-54	- Outcomes in study do not match those specified in this review protocol *Interval cancers (not detected by screening) not reported*
Wainberg, Sara and Husted, Janice (2004) Utilization of screening and preventive surgery among unaffected carriers of a BRCA1 or BRCA2 gene mutation. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 13(12): 1989-95	- Systematic review used as source of primary studies
Yang, Kathleen Y, Caughey, Aaron B, Little, Sarah E et al. (2011) A cost-effectiveness analysis of prophylactic surgery versus gynecologic surveillance for women from hereditary	- Study design does not match that specified in this review protocol

Study	Reason for exclusion
non-polyposis colorectal cancer (HNPCC) Families. Familial cancer 10(3): 535-43	*A theoretical population of women with Lynch Syndrome at age 30 was used for the analysis*

RRSO: risk-reducing salpingo-oophorectomy

Excluded economic studies

See Supplement 2 for the list of excluded studies across all reviews.

Appendix K Research recommendations – full details

Research recommendations for review question: What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

K.1.1 Research recommendation

What are the long-term benefits and risks of ovarian cancer surveillance for people at increased risk of familial ovarian cancer?

K.1.2 Why this is important

Although risk reducing surgery is recommended in women at increased risk of ovarian cancer, women may defer this surgery because they wish to preserve their fertility or do not want surgery, or they are not well enough to undergo it. The proposed benefit of surveillance for ovarian cancer in those with a familial cancer risk is to improve survival by detecting disease earlier. Surveillance however is not without risks as it can give false positive results leading to unnecessary surgery and false negative results in which a cancer is missed. Additionally, this may be associated with increased anxiety and psychological distress.

K.1.3 Rationale for research recommendation

Table 9: Research recommendation rationale

Research question	
Why is this needed	
Importance to 'patients' or the population	Importance to patients is through the early identification detection of ovarian cancer at a pre-symptomatic stage, with potentially better treatment outcome. This would enable these women to make informed decisions about the risks of deferring RRSO.
Relevance to NICE guidance	The relative absence of evidence regarding longer term outcomes of surveillance and lack of data on survival impact currently restricts NICE guidance from making firm recommendations in this area. The outcome of this research would allow such recommendations to be developed and become part of NICE guidance.
Relevance to the NHS	The early detection of ovarian cancer would fit with the NHS Long Term Plan ambitions for cancer.
National priorities	Cancer survival is a key priority for patients and the government, as stated in documents such as the NHS long term plan for cancer and NHS Clinically-led review of NHS cancer standards: models of care and management.
Current evidence base	Current evidence is limited regarding the long-term risks and benefits of surveillance. While downstaging of ovarian cancer has been demonstrated there is no data on survival benefit.
Equality	Access to information on surveillance may be different in women from different ethnic and socio-economic backgrounds. Research to explore this question could increase inclusivity and reduce disparity in health outcomes.
Feasibility	Randomised study of surveillance versus RRSO or no surveillance would not be ethical or acceptable in this high risk group. Longer term follow-up of observational or cohort surveillance studies may be possible.

Research question	
	Whilst the committee strongly encourage research in women with equality characteristics, they also noted that this would require large numbers and that this would likely make it less feasible than a study open to all.
Other comments	None

K.1.4 Modified PICO table

Table 10: Research recommendation modified PICO table

Criterion	Explanation
Population	Women at increased risk of ovarian cancer (because of a pathogenic variant: BRCA1, BRCA2, RAD51C, RAD51D, BRIP1 and PALB2) in who choose to delay or not have risk-reducing surgery. The committee agreed that research would be particularly welcome in groups of people with characteristics under the Equality 2010 Act (for example trans-men and non-binary people register female at birth or people from different ethnic backgrounds).
Intervention	Surveillance for ovarian cancer using serial biomarker (for example CA125 and/or other novel biomarker or multi-marker) based testing algorithm or strategies
Comparator	Standard care (which can include review appointment but not risk-reducing surgery): matched to intervention group on important confounders, such as level of risk, age, lifestyle factors associated with cancer)

Outcomes	• Quality of life
	• Survival:
	  ○ cancer specific survival
	  ○ overall survival
	• Ovarian cancer:
	  ○ incidence
	  ○ stage at diagnosis
	  ○ histological type
	• Treatment related adverse effects and test related morbidity
	• Surgical outcomes including R0 resection rates and morbidity.
	• Chemotherapy usage and outcomes
	• Psychological outcomes and wellbeing including:
	• healthcare use
	• cost-effectiveness

Study design	Prospective and/or combined retrospective cohort studies
Timeframe	5 to 15 years follow-up (although period of surveillance may be shorter)
Additional information	None

Appendix L Testimony from expert witness

Testimony from expert witness for review question: What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

Section A: Developer to complete	
Name:	Professor Alistair McGuire
Role:	Academic
Institution/Organisation (where applicable):	LSE, Houghton Street, London WC2A 2AE
Guideline title:	**Ovarian cancer: identifying and managing familial and genetic risk**
Guideline Committee:	Guideline committee meeting 9 (February 2023)
Subject of expert testimony:	Cost-effectiveness in the ALDO trial (surveillance for *BRCA* population)
Evidence gaps or uncertainties:	What are the benefits and risks of surveillance for women at increased risk of familial ovarian cancer?

One of the key areas of interest identified during scoping for this guideline was the benefits and risks of surveillance for women at increased risk of familial ovarian cancer. Not all women undergo risk-reducing surgery as they may wish to preserve their fertility, choose to avoid surgery or are not well enough to undergo surgery. The proposed benefit of surveillance for ovarian cancer in those with familial cancer risk is to improve survival by detecting disease earlier. Surveillance, however, is not without risks as it can give false positives leading to unnecessary surgery and false positives in which cancer is missed.

The review question covering the benefits and risks of surveillance found some limited evidence which showed no detrimental effect on health-related quality of life in those undergoing surveillance. However, based on the evidence and committee expert opinion, it was agreed that false positive surveillance test results (which were reported in several studies) might have a negative impact on health-related quality of life, for example, increased anxiety.

The diagnostic performance characteristics of most of the surveillance methods had wide confidence intervals, meaning there is a risk of false negative and false positive results, which would have a detrimental impact on people's well-being either because the cancer was missed or the test suggested cancer which was wrongly diagnosed. The test with the best performance characteristics in relation to false positive and false negative rates was CA-125 and the ROCA Test. There was also some evidence of cancer downstaging. However, there was no difference in mortality outcomes. The

committee also noted that downstaging might mean that some women may not be eligible to effective PARPi treatment due to current eligibility criteria.

The review of existing economic evidence found three non-UK studies which compared intensified ovarian and breast cancer surveillance with different risk-reducing strategies in *BRCA* mutation carriers. There was no economic evidence comparing different surveillance strategies or comparing surveillance to a no-surveillance alternative. No surveillance comparator is important since not all women undergo risk-reducing surgery for the reasons outlined above. Also, there was no existing economic evidence examining the cost-effectiveness of surveillance that utilised the ROCA Test. However, the committee identified an ongoing study that modelled the cost-effectiveness of surveillance of the ROCA Test in the ALDO trial in *BRCA* mutation carriers. The expert testimony is in relation to this economic study.

Section B: Expert to complete

Summary testimony:

This testimony relates to the economic modelling, based around a calculation of an Incremental Cost-Effectiveness Ratio (ICER), to accompany the clinical evidence from the ALDO trial. The purpose of this trial was to establish the 'real-world' performance of Ovarian Cancer (OC) surveillance in women with pathogenic germline *BRCA1/2* variants deferring risk-reducing salpingo-oophorectomy (RRSO). This was a one-arm, one year trial run across 875 female *BRCA1/2*-heterozygotes, recruited at 13 UK centres and via a media campaign, who underwent 4-monthly surveillance with the ROCA Test. Surveillance performance was calculated with modelling of occult cancers detected at RRSO. An ICER was calculated using Markov population cohort simulation. The trial found 8 OCs occurred during 1277 women screen years: 2 occult OCs at RRSO (both stage 1a), and 6 screen-detected; 3 of 6 (50%) were ≤stage 3a and 5 of 6 (83%) were completely surgically cytoreduced. Modelled sensitivity, specificity, PPV and NPV for OC were 87.5% (95%CI, 47.3-99.7), 99.9% (99.9-100), 75% (34.9-96.8) and 99.9% (99.9-100) respectively. The predicted number of quality-adjusted life-years gained by surveillance was 0.235 with an ICER indicating cost saving of £138,149/QALY. Sensitivity analysis on the price of the ROCA Test, the age of initiating surveillance and the detection rate did not change the cost-saving result.

References:

Philpott, S., Raikou, M., Manchanda, R., Lockley, M., Singh, N., Scott, M., et al., The avoiding late diagnosis of ovarian cancer (ALDO) project; a pilot national surveillance programme for women with pathogenic germline variants in BRCA1 and BRCA2, Journal of medical genetics, 60, 440-49, 2023

Disclosure:

None